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CERTAIN PATHOLOGICAL ASPECTS OF NEUROSYPHILIS.

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INTRODUCTION.

DURING the last two decades earlier recognition of the various forms of neurosyphilis has resulted in much clinical and subsequent pathological study of this manifold disorder. The discovery in 1917 of the beneficial effects of induced malaria in general paralysis has especially stimulated a revival of interest in that malady. Neuropathologists have been particularly active during the last five years in investigating cases of general paralysis which have been treated by malaria, and they have produced exhaustive but conflicting reports both on the histopathology of the brain and on the mode of operation of the treatment.

Little attention has, however, recently been paid to the histopathology of cases of early general paralysis thoroughly treated by means other than malaria. The histological comparison between malarial and non-malarial treated cases rests on the classical descriptions of such

early workers as Nissl, Alzheimer, Achucarro and Mott, who saw only the most severe forms of untreated or inadequately treated cases.

Further, possible differences in the histopathological picture of general paralysis at different periods of life have not hitherto been generally considered. As Critchley has lately shown, the tissues of the brain in the elderly differ both in their minute structure and in their reactions from those of the young subject.

Freeman has remarked on our scanty knowledge of the extra-cerebral pathology of neurosyphilis, particularly of general paralysis, but he himself has made a valuable contribution to it.

The investigation of which this study forms a part was planned along lines suggested by the foregoing brief sketch of a few of the fertile sources of inquiry available to the pathologist in the field of neurosyphilis.

The material at my disposal consisted of thirty-six cases: twenty-eight of general paralysis and tabo-paresis, and eight of tabes dorsalis. Thirty-three of these had been patients in the National Hospital for Diseases of the Nervous System, Queen Square, and I am indebted to members of the honorary staff of this hospital for permission to record them. I have also to thank Dr. Poynton who has kindly allowed me to examine pathologically and quote a case of a child with congenital general paralysis who was under his care at the Hospital for Sick Children, Great Ormond Street; and Dr. G. Griffiths who kindly supplied me with pathological material from, and clinical notes of, two cases at Cheddleton Mental Hospital.

Post-mortem reports have been quoted somewhat fully, as in some cases which came to post-mortem before this investigation was begun in 1928 no microscopic examination of the viscera was made. I am greatly indebted to Dr. J. Godwin Greenfield for allowing me to use his reports on the post-mortem examinations and on the cerebrospinal fluids.

As it would be of little interest to present complete pathological reports of all the cases examined, a few illustrative cases have been recorded. These serve to demonstrate especially the lesions found in mild and severe types of paresis not treated by malaria: those found immediately after or shortly after malarial therapy; and those found in the case of a patient who died during a relapse. A report of the one congenital case has been included for comparison with the case of the oldest patient. Observations, however, have been based on the whole series, not on these particular cases only, and where it has seemed necessary to refer to other cases in order to elucidate a certain point, this has been done.

Pathological Reports.

Sections were made in all cases from the precentral and anterior frontal areas of the brain and wherever possible from the basal ganglia, mid-brain and medulla. The spinal cord was examined if the clinical symptoms and signs indicated the presence of a lesion in it, or if evidence of disease other than a slight arachnoiditis was found. A microscopical examination of the viscera, especially of the liver and aorta, was made wherever possible, actually in eleven cases.

The following methods were used on sections of the cerebral cortex from every case: The Prussian-blue method for the demonstration of iron-containing pigment and a method for demonstrating microglia on frozen sections; iron-hæmatoxylin with van Gieson's counterstain and Nissl's toluidin blue method on celloidin sections. Where material fixed in formol-bromide was available (as it was from 1927 onwards), this was used for Cajal's neuroglial method and for Hortega's microglial method. In lieu of material fixed in formol-bromide, that fixed in formol saline was used for the demonstration of microglia by Cone and Penfield's modification of Hortega's method, which proved satisfactory. Several blocks of the prefrontal and frontal cortex from each case were stained for spirochætes by Jahnel's method, and in two cases sections of blocks from the mid-brain and medulla stained by Jahnel's method were cut, every tenth or fifteenth section being mounted and examined. Control material from a brain containing many spirochætes was stained for comparison at the same time as most of the other sections. Spirochætes in the control material did not once fail to stain by Jahnel's method. Latterly Kanzler's method for the demonstration of spirochætes in single frozen sections was used also, the results being controlled by staining the remainder of the same block of tissue by Jahnel's method. Affected portions of the aorta were stained for spirochætes in all cases in which a definite mesaortitis was present, whether spirochætes had been found in the cerebral cortex or not.

Case 1, *illustrating a mild type of paresis with co-existent tabes.*

J. M., a married man, aged 55, was admitted to the National Hospital under the care of Dr. Riddoch on October 6, 1927. He complained of loss of memory and difficulty in walking for one year. According to his wife the patient had become languid and easily tired, but had always protested that he was quite well. His speech had become tremulous; sometimes he was unwilling to speak and sometimes he was communicative. He had fallen whilst walking on several occasions, and had had one attack of "shaking" which lasted for only five minutes, during which time he had been dazed.

On examination the patient was found to be drowsy but fairly co-operative. Speech was tremulous and slurring, but there was no tremor of the tongue or hands. The pupils were small and irregular in outline and inactive to light, but they reacted well on convergence. There was a generalized blunting of sensation to pain and the sense of deep pain was lost in the calves. Vibration sense was abolished over the radial styloids and tibial malleoli. The sense of position and passive movement were normal. The legs were very ataxic. The knee-jerks and ankle-jerks were absent and the plantar responses were flexor.

The heart appeared to be within normal limits as regards size and no murmurs were detected. The pulse was regular in rate and rhythm and the radial artery felt healthy. The patient had a stricture of the urethra and this was associated with some infection of the bladder. The report on the cerebro-spinal fluid was: cells, 8 per c.mm.: 40 per cent. large mononuclears, a few large granular cells. Total protein 0·06 per cent. Nonne-Apelt strongly positive, Pandy strongly positive. Lange 3443333211. W.R. positive, in fluid 4444, in blood 4444. The patient had two fits with rigors whilst in hospital and died suddenly on October 28, three hours after the second. A post-mortem examination was performed twelve hours after death by Dr. J. G. Greenfield. Over the vertex of the brain the arachnoid ran firmly over the sulci, which were slightly widened. There was great arachnoidal proliferation in the region of the Paccionian granulations. Over the dorsal surface of the spinal cord there was considerable thickening of the arachnoid, especially in the cervical region, where several whitish, thickened patches were seen. In the chest there was considerable early fibrinous adhesion of both lungs to the pleura with congestion of the lower lobes. The heart muscle and valves appeared healthy. The right ventricle and pulmonary artery contained a firm red coagulum about 1¼ in. long and less than ½ in. thick. The aorta was covered with whitish cushions of syphilitic aortitis. The liver was normal. The spleen and kidneys were congested. The bladder was very thick-walled and the veins under the mucosa were congested. There was very little evidence of recent inflammation.

Microscopical examination.—The aorta showed proliferation of the intima; the vasa vasorum were thickened and slightly infiltrated with small round cells and plasma cells. There was no obvious destruction of the elastic tissue, but some accumulations of lymphocytes were seen between the elastic fibres. No spirochætes were found in the aorta.

In the brain much iron was present round the cortical vessels and in the processes of many microglial cells. There was an enormous increase in the number of microglial cells. Rod-cells were numerous and were distributed regularly at right angles to the surface. Many transitional forms of microglial cell were also present, particularly in relation to blood-vessels.

The meninges were greatly thickened and were heavily infiltrated, principally with plasma cells, though a few small lymphocytes and endothelial cells were also observed. The cortex contained a very large number of small

thick-walled vessels which in the more superficial layers of the grey matter were practically free from cellular infiltration. In the deeper layers and in the subjacent white matter several vessels were heavily infiltrated by small lymphocytes. Plasma cells were only occasionally seen. In the basal ganglia similar perivascular infiltrations were observed, particularly in the putamen. Rod cells, in the processes of which iron could be demonstrated, were present in large numbers in the putamen and in the caudate nucleus. There were slight degenerative changes in the nerve-cells of the thalamic nuclei. The vessels and nerve-cells in the mid-brain appeared healthy and no perivascular infiltration could be seen in this region.

There was a great loss of nerve-cells in the prefrontal and frontal cortex. Those which remained appeared for the most part healthy, but a few of the larger nerve-cells were undergoing neuronophagia. The cyto-architecture of the cortex was not greatly altered though the various layers were not so easy to distinguish from each other as in a normal cortex.

Spirochætes were found in one block of tissue from the right frontal region only. They were very few in number, seldom numbering more than one or two in a section. No spirochætes were seen in the meninges over the areas of the brain examined. No relationship of the spirochætes to blood-vessels or nerve-cells could be determined, and indeed the number of spirochætes present was so sparse that any such relationship would have been surprising. The type of spirochæte was the long form, some having as many as twenty spirals. No short or atypical forms were seen. The spirochætes occurred in the superficial and deep layers of the cortex but none were found in the white matter. Serial sections of the mid-brain and of the floor of the fourth ventricle failed to reveal spirochætes.

The spinal cord showed intense meningeal infiltration with plasma cells and lymphocytes, and degeneration of the middle root zone in the lumbar and dorsal regions.

Case 2, *illustrating a severe type of paresis.*

H. P., a male, aged 42, was admitted to the National Hospital under the care of Dr. Collier on August 22, 1924. He was diagnosed in the out-patient department as a typical case of general paralysis, when he one day had a generalized convulsion and was admitted to hospital in status epilepticus. He died two days later without regaining consciousness. His temperature just before death was 108·3° F.

On examination on the day of admission, the right pupil was found to be larger than the left. Neither reacted to light. The knee and ankle jerks were present. The right plantar response was extensor, the left flexor. The heart was not enlarged and no murmurs were heard. The pulse was rapid and remained at about 112 till death. The arteries were thickened. The report on the cerebrospinal fluid was as follows: Cells 25 per c.mm. Total protein 0·05 per cent. Nonne-Apelt positive. Lange 3444444321. W.R. positive, in fluid 4442, in blood 3210.

A post-mortem examination was performed twenty-four hours after death by Dr. J. G. Greenfield. The brain showed some basal meningitis but no apparent wasting of the convolutions. There was some thickening of the pia-arachnoid along the posterior surface of the cord with miliary gummata over the points of emergence of the lowest dorsal and lumbar roots. The lungs were healthy except for one or two small areas of inhalation pneumonia in each lung. The heart was large and flabby; its chambers were all dilated but not hypertrophied. In the aorta a patchy atheroma was present. The liver and kidneys were healthy. The spleen was slightly congested.

Microscopical examination.—The liver appeared normal except for fatty degeneration in a few cells. There were extensive confluent broncho-pneumonic changes in the lungs. In the aorta the intima was thickened; much of the elastic tissue in the media was replaced by fibrous tissue and the vasa vasorum were infiltrated with small lymphocytes.

Small deposits of iron were visible around the vessels in both the grey and the white matter of the brain, although the sections were stained six years after fixation. The microglial cells naturally did not give a strong reaction for iron after such prolonged fixation, and for that reason their processes could not be well demonstrated, but the processes of rod-cells were sufficiently well stained to show that a large number of these cells was present, and that many lay at right angles to the surface of the cortex. Intermediate, atypical forms of microglial cells were also present, particularly in the deeper layers of the cortex. Many atypical forms of astrocytes were also seen in addition to a general increase in the amount of neuroglia. These abnormal forms were well demonstrated by Jakob's anilin-blue, orange G method, the most obvious and frequent abnormality being a swelling of the cell body with shortening of the processes.

Meningeal thickening was very striking over the frontal cortex. In the depths of the sulci large collections of small lymphocytes could be seen; elsewhere in the meninges there was an exudate containing a number of plasma and endothelial cells as well as small lymphocytes. The cortex was very vascular and nearly every vessel was heavily infiltrated. Cellular infiltration was greater in this case than in any other of the series. Every vessel in both grey and white matter of the cortex had a dense perivascular cuff containing chiefly small lymphocytes, though a certain number of plasma cells were also visible around some vessels. It was not uncommon to see the lumen of a vessel almost obliterated by small lymphocytes. There was no formation of miliary gummata. In the putamen, the caudate nucleus and the thalamus perivascular infiltration was remarkable. In these areas the tissues had become highly vascularized, and even the smallest capillaries were ringed by large numbers of cells which extended from the perivascular spaces into the surrounding tissues. Most of these infiltrating cells were plasma cells and many had bi-lobed nuclei; a few plasma cells contained two and even three nuclei. Numerous small lymphocytes also were present. The globus pallidus was singularly free from cellular infiltration. Deposits of iron were found

round even tiny blood-vessels in the putamen and caudate nucleus; little was present round vessels in the thalamus. Finer deposits of iron were visible in the processes of the rod-cells which occurred in large numbers in the putamen and the thalamus. Numerous astrocytes were also visible in these situations; although it was not possible to demonstrate their processes they were identified by their typical nuclei. Many nerve-cells in the thalamic nuclei were degenerate and were surrounded by satellite microglial cells.

A similar type of perivascular infiltration was seen in the mid-brain, pons and medulla, but in sections through the mid-brain the vessels in the region of the oculo-motor nuclei appeared to be more densely "cuffed" than those in other parts of the sections. The cells of the third nerve nucleus were degenerating and one or two had already degenerated so far as to merit the title of "ghost-cells."

The cyto-architecture of the cortex was grossly disturbed. A large number of nerve-cells had disappeared and many of those which remained were being engulfed by satellite cells. It was impossible to distinguish the layers of the cortex.

An occasional spirochæte was found in sections from one block of tissue from the right frontal cortex (six blocks from the right prefrontal and frontal cortex were examined with negative results). The spirochætes showed no predilection for any particular layer of the cortex; they occurred in the superficial and the deep layers but not in the white matter. Seldom more than two or three could be found in a section. I could not find any in the walls of the blood-vessels or in nerve-cells, and no "swarms" or aggregations of spirochætes were observed. The type of spirochætes present was the short one, having about seven spirals and often ending in a terminal bulb or knob. No ring or other atypical forms were seen. A few long spirochætes having about fourteen spirals were present in the sections examined but were very scanty, seldom more than one being seen in two or three sections. The floor of the fourth ventricle with its ependymal granulations was searched in serial section for spirochætes with negative results.

Case 6, illustrating early post-malarial appearances.

S. A., a married man, aged 33, was admitted to the National Hospital on March 29, 1927, under the care of Dr. Stewart. As the patient was unable to give a reliable history the following account of his illness was obtained from his wife: One year previously the patient had become strange in his manner, childish and bad-tempered. He soon became "impossible to live with." He had had transient attacks of weakness on the left side during the past two years.

On examination, the mental condition of the patient was poor, and his memory was bad. His speech was slurring and tremulous and there was a coarse tremor of the tongue and a fine tremor of the outstretched hands. The pupils were eccentric and oval in shape; they reacted poorly to light and on convergence. The patient was deaf on the right side. On elevation of the

palate the uvula was drawn to the right side. The palatal reflex was absent. Power was greater in the right arm than the left, but better in the left leg than the right. Sensation appeared normal. The knee-jerks were present. The ankle-jerks were very brisk. The plantar responses were flexor. The heart was not enlarged and no adventitious sounds were heard.

The patient was inoculated with malarial blood and eight days after the inoculation he had a fit with loss of consciousness. On recovery there was increased weakness and spasticity of the left arm and leg with a doubtful extensor response on the left side. The patient had six rigors in all, four before the fit and two after, and died on June 11, the twelfth day after the inoculation. The report on the cerebrospinal fluid was: Cells 77 per c.mm., 4 per cent. large mononuclears, 1 per cent. polymorphonuclears. Total protein 0·1 per cent. Nonne-Apelt strongly positive, Pandy strongly positive. Lange 2455553321. Wassermann reaction positive, in fluid 4444, in blood 4441.

A post-mortem examination was made by Dr. J. G. Greenfield twelve hours after death. On removal of the brain and spinal cord the frontal lobes appeared much shrunken and the meninges over them were thickened. Miliary gummata were seen over the sulci. The arachnoid over the dorsal surface of the spinal cord was thickened. Both lungs were congested and the right lung was adherent to the pleura. The heart was not enlarged and only a few atheromatous plaques were seen on the aorta. The liver and kidneys were healthy. The spleen was very much enlarged and softened. The pulp contained no parasites in films.

Microscopical examination.—In the aorta there was perivascular infiltration of vasa vasorum with small lymphocytes. Some small collections of lymphocytes were present in the media. No spirochætes were found.

Brain: Nearly every vessel in the cerebral cortex was heavily ringed by deposits of iron which occurred in large clumps. A little iron was seen in the processes of the microglial cells. (The sections were stained for iron three years after fixation in formol saline and an intense Prussian-blue reaction of the fine granular deposits of iron in the microglial cells could not therefore be expected). An enormous number of rod-cells were present in the cortex. For the most part they ran in parallel rows at right angles to the surface. Rod-cells were especially numerous in the more superficial layers of the cortex: in the deeper layers there were a large number of intermediate forms between the true rod-cell and the normal microglial cell. These forms were particularly evident around blood-vessels. The cerebral meninges were hyperplastic and heavily infiltrated with plasma cells. A few lymphocytes and endothelial cells were also seen in the exudate. But in the depths of the sulci large accumulations of small lymphocytes were present, and in these masses no plasma cells were found. The cortex was extremely vascular; it appeared almost "riddled" with small thinly-walled blood-vessels. The walls of the larger vessels were thickened. The vessels in the more superficial layers of the cortex were only slightly infiltrated, the infiltrating cells being small lymphocytes. In the deeper layers of the grey matter, and more especially in the white matter, the

large vessels were surrounded by many layers of small lymphocytes. Practically no plasma cells were observed in these infiltrations. In the basal ganglia the vessels appeared to be much thickened, and around a few there was slight infiltration with small lymphocytes. This was especially evident in the caudate nucleus, where also there was proliferation of the microglia with rod-cell formation. Very small deposits of iron were seen in the processes of rod-cells and around blood-vessels. There was a definite loss of nerve-cells in the cortex but those which remained appeared healthy. The cortical laminæ were easily distinguishable. No spirochætes were found in this case.

Case 25, illustrating the lesions found two and a half months after malarial treatment.

H. G., a married woman, aged 45, was admitted under the care of Dr. Grainger Stewart, on March 9, 1926. She was unable to give a coherent account of her illness, but the following history was elicited from her husband: Her illness was dated from a "nervous breakdown" two years previously. Speech had been tremulous and difficult for about six months and for the same time the patient had been depressed and irritable. The patient's first husband had died in an asylum of general paralysis. By him she had had three children, who were alive and well, and had had one miscarriage. By her second husband there had been no children and no miscarriages.

On examination the patient was found to be depressed and disorientated in time. Memory and cerebration were poor. Speech was tremulous and a coarse tremor of the tongue was observed. The right pupil was larger than the left. Both reacted poorly to light but well on convergence. There was some blunting of sensation to pain over the "snout" area of the face, but pain sensibility was otherwise normal. Vibration sense was diminished over the tibial malleoli and the ulna. The knee-jerks were brisk; the ankle-jerks were absent. The right plantar response was a doubtful extensor, the left a definite extensor. Nothing abnormal was detected in the cardio-vascular system. The report on the cerebrospinal fluid was: Cells 70 per c.mm. 10 per cent. large mononuclears. Total protein 0·06 per cent. Nonne-Apelt strongly positive. Pandy strongly positive. Lange 4555543321. W.R. positive 4444 in fluid, 4444 in blood. The patient was given tertian malaria intravenously and died nine weeks later of meningitis secondary to bedsores. (The temperature chart is not now obtainable.)

A post-mortem examination was performed twelve hours after death by Dr. J. G. Greenfield. Large gangrenous bedsores were present over the sacrum and right hip. On removal of the brain very much pus, smelling putrid like a bed sore, was present throughout the whole subdural space, even over the vertex of the brain. In contrast to this there was very little subarachnoid pus, but the subarachnoid space was everywhere infiltrated with chronic meningitis. Over the vertex the sulci were widened. The arteries of the base of the brain showed a little atheroma in the form of thickened gelatinous plaques. The chest was normal except for a patchy collapse of the lungs at their bases. There was a small amount of pericardial fluid present. The

heart was healthy. The ascending aorta was normal, but the descending aorta showed numerous gelatinous plaques of atheroma. The liver was pale and firm and apparently the seat of an early monolobular cirrhosis. The spleen was very much enlarged and dark in colour. The Malpighian bodies were evident. The kidneys were healthy. The uterus was large and thick-walled. The ovaries were healthy.

Microscopical examination.—The liver showed advanced fatty degeneration of the liver cells. There was no evidence of cirrhosis.

In the cerebral cortex there were large deposits of iron around the cortical vessels and a little iron was seen in the processes of a few microglial cells (sections stained four years after formalin fixation). A very large amount of protoplasmic neuroglia was present in the cortex. Many vessels were surrounded by astrocytes, the numerous foot plates of which were attached to the vessel walls. The microglia was greatly proliferated. Many rod-cells were present; some were arranged in parallel rows at right angles to the cortex, others were scattered irregularly through the cortex. Many intermediate forms of microglial cells were observed; some had oval nuclei with a few processes, others had elongated nuclei with many processes, but all stages between the typically normal microglial cell and the rod cell could be found. Intermediate forms were particularly evident in the neighbourhood of blood-vessels.

The meningeal changes were those of a purulent meningitis and bore no relation to the syphilitic lesions in the brain. The cortex was very vascular and the walls of the vessels were thickened. There was little infiltration around the vessels in the superficial layers of the cortex, but at the junction of grey and white matter and in the white matter there was a moderate amount of infiltration with small lymphocytes and plasma cells. In the basal ganglia there were large deposits of calcium in the media of the vessels, which were greatly thickened. A few vessels showed perivascular cuffing, chiefly with small lymphocytes. Many rod-cells were present in the putamen and the caudate nucleus and in the thalamus, but no iron could be demonstrated in their processes. Large amounts of iron were present, however, around the vessels in these regions. A few cells in the thalamus were undergoing degenerative changes. The vessels in the medulla were slightly infiltrated with small lymphocytes, but the vessels in the mid-brain seemed unaffected. The nerve-cells in the mid-brain appeared healthy.

There was a gross loss of nerve-cells in the anterior frontal and frontal cortex. Those which remained retained a normal structure, but their distribution was so irregular that the cortical layers merged one into the other and it was impossible to distinguish the different laminæ.

No spirochætes were found in this case.

Case 28, *illustrating the lesions found twenty months after the last malarial inoculation.*

E. B., a male, aged 48, was admitted to Cheddleton Mental Hospital in June, 1927, with a history of increasing fabrication for three years and strange behaviour for six months.

On examination his physical condition was fair. He had wild delusions of grandeur. His speech was slurred and his tongue was tremulous. The pupils were equal and gave the Argyll Robertson reaction. The knee-jerks and ankle-jerks were absent and gait was unsteady. The Wassermann reaction was positive in the cerebrospinal fluid and the blood. Malarial inoculations were given on July 7, 1927, September 26, 1927, July 30, 1928, April 9, 1929, May 13, 1929. Parasites were found in the blood in August, 1927, April, 1929, and June, 1929. A course of seven injections of tryparsamide was given from November, 1927, and mercury with potassium iodide was given from July, 1929, onwards. The mental symptoms persisted unaltered, though the physical condition remained good. Death followed a seizure in February, 1931.

At post-mortem an increased amount of fluid was found in the ventricles. The brain was congested and the gyri were flattened. There was some atheroma of the thoracic and abdominal aorta.

Microscopical examination.—Large deposits of iron were found around most cortical vessels and in the processes of the microglial cells. There was an enormous overgrowth of microglia, especially in the superficial layers of the cortex. Only a few typical rod-cells were seen and these did not present an orderly arrangement relative to the surface of the cortex, but many atypical forms of microglial cell were visible, the commonest being an elongated cell with a large number of processes. Many microglial cells were acting as satellites to nerve-cells and appeared to be engulfing them. By prolonging the impregnation with silver in the method used to demonstrate microglia, the processes of the protoplasmic astrocytes were sufficiently well stained to allow of the statement that the protoplasmic neuroglia was greatly increased in amount.

The meninges were hyperplastic and heavily infiltrated and in the depths of the sulci there were large accumulations of small lymphocytes. Elsewhere in the meninges the cells were mainly plasma cells and endothelial cells. The cortex was very vascular and the walls of the cortical vessels were much thickened. Most vessels, especially in the deepest layers of the cortex and in the white matter, were surrounded by wide cuffs of cells of which plasma cells formed a certain proportion, though the majority were small lymphocytes.

Very few nerve-cells remained in the anterior frontal and motor cortex, and most of these were surrounded by satellite cells. The pattern of the cortex was grossly distorted and it was almost impossible to distinguish the separate layers.

Enormous numbers of spirochætes were present in several blocks of tissue from the prefrontal cortex, but in other blocks from the frontal region not one single spirochæte could be found. Although the typical "swarms" described by Jahnel were not observed, distinct aggregations of 40 to 50 spirochætes were seen in some parts of sections. The most common arrangement was the diffuse one in which spirochætes were scattered throughout the section and appeared in all layers of the cortex. A number of spirochætes were seen in

relation to the cortical vessels, the walls of which contained many, but only once was I able to satisfy myself that a spirochæte lay actually in the lumen of a vessel. Even in sections cut at 3 μ it is difficult to be certain that spirochætes are in the lumen of the vessel and are not merely lying above or below the vessel, but in one vessel cut longitudinally the most careful focusing did not reveal any discrepancy between the level of the vessel and that of the spirochætes in its lumen. I could determine no relationship of spirochætes to nerve-cells. The limiting membrane of nerve-cells apparently presents an impenetrable barrier to the spirochætes; for although clusters of spirochætes surrounded nerve-cells in many sections, nowhere could I find a spirochæte inside a nerve-cell or in the process of passing through its wall. Both long and short forms of spirochætes were present, but all forms were typical, i.e., they exhibited regular, even spirals. I did not observe any of the atypical forms which Jahnel has described in the brain and Warthin in the aorta. The spirochætes were limited to the cortical grey matter; none were found in the white matter of the cortex or in the ependymal granulations in the floor of the fourth ventricle, which was the only other part of the brain available for section.

Case 27, illustrating congenital paresis treated by malaria; death ten months after treatment.

E. W., a male child, aged 8 years and 10 months, was admitted to the Hospital for Sick Children, Great Ormond Street, under the care of Dr. Poynton, in February, 1928, with a history of fits and mental deterioration beginning at the age of 6 years. His mother had a very strongly positive Wassermann reaction. On examination the child was abnormally loquacious and of poor mentality. The pupils reacted to light. The knee and ankle jerks were present and the plantar responses were flexor. The report on the cerebrospinal fluid was: Cells 5 per c.mm., all mononuclears; protein, 0·025 per cent; Lange reaction gave a paretic curve; Wassermann reaction strongly positive.

The child was given malarial blood hypodermically on February 11, and the fever was terminated by quinine on March 16. When readmitted for observation on November 26, 1928, no alteration in the mental condition was noted. The knee and ankle jerks were then present. The cerebrospinal fluid contained 5 cells per c.mm., all mononuclears; globulin was greatly reduced in amount; Lange 5555443100; Wassermann reaction positive 4444. The child was then given salvarsanized serum by the cisternal route. After cisternal puncture on December 13, 1928, he passed into status epilepticus and died in coma.

At post-mortem examination the bones of the vault of the skull were found to be very much thickened. There was great congestion of the veins of the scalp. The dura was very adherent to the skull in the region of the longitudinal sinus. The dura and pia-arachnoid were much thickened. The brain was deeply congested. There was very little flattening of the convolutions, but wide dilatation of the lateral ventricles. Granular ependymitis was seen in the floor of the fourth ventricle. The vessels at the base of the brain were

thicker than normal. The spinal cord appeared normal. The thymus was very large and weighed 32 grm. Both lungs were very congested. The heart showed a small patch of atheroma on the mitral valve and another patch near the opening of the right coronary artery. The liver and spleen were both enlarged, and the spleen was adherent to surrounding structures. On section it was soft and diffluent. The kidneys were very congested. The suprarenals and testes appeared normal.

Microscopical examination.—The liver showed fatty degeneration of a few cells and the formation of fine strands of fibrous tissue between the columns of cells. It was greatly congested, all the blood-vessels being widely dilated.

In the brain, a small quantity of iron was seen in the processes of the microglial cells and around blood-vessels. There was a large increase in the number of microglial cells, especially in the neighbourhood of the cortical vessels. A fair number of rod-cells were present, but those did not show any constant arrangement relative to the surface of the cortex. Many abnormal types of microglia cells with indented nuclei were observed. The cerebral meninges were much thickened and a cellular exudate consisting mainly of plasma cells and large lymphocytes was present. The cortex was exceedingly vascular and the walls of many of the vessels were evidently thickened. Only very slight lymphocytic perivascular infiltration was observed around a few vessels; for the most part the vessels were singularly free from infiltrations. There were a few ependymal granulations in the floor of the upper part of the fourth ventricle. The vessels in the vicinity of the ventricle were thickened and surrounded by "cuffs" of cells, mainly lymphocytes.

The nerve-cells in the anterior frontal cortex appeared to be greatly diminished in number but those which remained were normal. Lamination of the cortex was not disturbed.

No spirochætes were found in this case.

Histological Features of Malarial Treated and Non-Malarial Treated Cases of General Paralysis.

Before discussing the chief points on which various workers differ in their observations on the histology of general paralysis treated by malaria, it appears relevant to consider briefly the outstanding histological features of a typical case untreated by malaria.

The reactions of the tissues of the brain in general paralysis fall into two groups, the ectodermal and the mesodermal. The ectodermal group comprises both degenerative and proliferative changes; degeneration of the nerve-cells and fibres of the cerebral cortex, especially in the frontal region, proliferation of the cortical neuroglia, particularly of the subpial fibrous neuroglia, and of the protoplasmic neuroglia in the grey matter. The mesodermal reactions are those of the wandering cells, of the vessels, and of Hortega's "third element," which he believes to be

mesodermal in origin. The wandering cells manifest their activity by perivascular infiltration of the cortical vessels and by infiltration of the meninges, though neither reaction is specific for general paralysis or for syphilis. The high proportion of plasma cells in the infiltrations, which for a long time was considered pathognomonic of general paralysis, may occur in many other conditions, notably in epidemic encephalitis. The arteries of the cortex may show the changes of endarteritis obliterans, but Jakob holds the view that these changes are not constant. The reactions of the Hortega cells, or microglia, are highly characteristic, and one particular reaction, the storage of an iron-containing pigment, is, in the absence of hæmorrhage and of trypanosomiasis, specific for general paralysis. The formation of large numbers of "Stäbchenzellen," or rod-cells, in general paralysis, was first described by Nissl and Achucarro. Spielmeyer emphasized their characteristic appearance and the fact that they were rarely present in other diseases of the nervous system. Hortega traced their origin to mesodermal elements and related them to the reticulo-endothelial cells which are the "scavenger" cells of the body. It is not surprising, therefore, to find that the rod-cells play an important role in "scavenging" in the nervous system.

The picking up, storage and transport of a pigment containing iron, probably hæmosiderin, is one of the chief functions of the microglia, and the presence of a substance in the rod-cells which gives a Prussian-blue reaction is a diagnostic histological feature in general paralysis. Hayashi, in 1913, was one of the first to observe iron in the rod-cells in general paralysis. Lubarsch, in 1917, described it in the rod-cells and in the adventitial spaces of the blood-vessels in the cortex in over a hundred cases. Spatz and Metz, who have done a great deal of work on the subject of the relation of the microglia to the storage and transport of iron in the nervous system, came to the conclusion that in general paralysis the microglia constitutes the sole means of transport of iron from blood-vessels to the tissues, or *vice versa*. The disturbance in the metabolism of iron which leads to the abnormal storage is as yet undetermined. Spatz and Metz suggested a disproportion between supply and utilization; Proescher and Arkush conjectured that the iron seen in the microglial cells in general paralysis came from the nuclei of disintegrating nerve-cells and, being an abnormal form, was more difficult to remove. This supposition is unlikely, seeing that in conditions where there is great destruction of nerve-cells no iron can be found in the microglia.

Jakob did not venture on an explanation of why iron should be so increased in amount in general paralysis, he merely alluded to its value as a diagnostic feature. Lasarew, and Proescher and Arkush, also stressed the utility of demonstrating iron in the microglial cells as a quick method for the diagnosis of general paralysis. The advantages of this method have not yet been generally recognized in this country. Within half an hour of brain section the diagnosis of general paralysis can be made with certainty in all but a very few cases. The reaction for iron not only gives the iron content of the microglial cells by outlining their presence, but it also shows the general distribution of the microglia.

Jakob found that the iron content of the rod-cells ran parallel with the amount of perivascular infiltration. Where there was much perivascular infiltration and much iron in the adventitial spaces of the vessels, there was also a large amount in the microglia. In cases of stationary paralysis and also in cases which succumbed rapidly, Jakob did not find the typical reaction. Proescher and Arkush, on the other hand, found a large amount of iron present in cases which ran a rapid course. Those cases which died in or just after epileptic seizures gave a specially strong iron reaction.

The question of the iron reaction after malarial treatment may be shortly dealt with here as few observations are recorded. Schultze and Steiner mentioned that the Prussian-blue reaction was scanty, but they gave no details as to the length of time the patient survived the treatment. Wilson found that the iron reaction was stronger in the cortex of patients dying within six weeks of the treatment than in cases not treated by malaria, and he attributed this increase to an increased permeability of the vessels. Thereafter a gradual diminution occurred, in the amount of iron around blood-vessels and in the microglial cells, which Wilson supposed was due to decreased permeability of the vessels.

In my series, the Prussian-blue reaction was performed in twenty-seven out of the twenty-eight cases. Of the four cases not treated by malaria large amounts of iron were present around the cortical vessels in three cases (Cases 1, 2 and 3); none was observed in the fourth (Case 4). In Case 1, there was a very large amount in the microglial cells. In Cases 2 and 3, none could be seen in the microglial cells, but as the sections were stained six and eight years after death respectively, the negative results are of no significance. Case 4 presented an interesting picture of complete failure of mesodermal reaction. No iron could be demonstrated in the microglial cells, only a very few rod-cells were present and there was no perivascular infiltration whatsoever in the

cortex. The loss of nerve-cells was striking, and the case though clinically a typical general paralytic was definitely atypical pathologically. It is of interest that the cerebrospinal fluid of this case did not show a paretic Lange curve.

Of the twenty-three malarial treated cases, all except one (Case 21) showed heavy deposits of iron around the cortical vessels. Three failed to give the iron reaction in the microglial cells, but of these, two (Cases 10 and 13), were examined six and seven years after fixation. The other case (Case 21) showed no iron around the vessels, and was of interest in that in spite of a large increase in the amount of microglia very few rod-cells were present, and no perivascular infiltration was seen in the grey matter of the cortex and only a little in the white matter. The nerve-cells were diminished in number and there was a large increase in the number of protoplasmic astrocytes. Here also there appeared to be a failure of mesodermal reaction in spite of malarial treatment. The clinical picture was that of early general paralysis, cerebral symptoms having been present for only nine weeks. It is noteworthy that in this case also the cerebrospinal fluid did not give a paretic Lange curve. The condition of the blood-vessels and meninges did not warrant a pathological diagnosis of meningo-vascular cerebral syphilis in this case or in Case 4, but it would be equally incorrect to describe these two cases as cases of true general paralysis. The other cases treated by malaria all showed varying amounts of iron in the microglial cells, and I could determine no distinction in the amount present between those cases which succumbed during the very early days following malarial treatment and those which lived for nine weeks, ten months and twenty months respectively. (The last case, No. 28, died immediately following a seizure and had long given clinical evidence that the effects of his five malarial inoculations had been transient). There was no evidence that the amount of iron present in the microglial cells was dependent upon the amount of cellular infiltration. Much iron was often present when the perivascular infiltration was slight, as in Cases 22 and 23.

From the results of my experience with the Prussian-blue reaction in this series of cases, it is possible to express the opinion that the reaction is one on which the pathological diagnosis of general paralysis can be based, given that the material is examined within a reasonable time after formalin fixation (within six months allows of a safe margin for differences in technique).

Records of the histopathology of the brain after malarial treatment

have mounted steadily during the past few years, and reference will be made only to the larger series which have been published, as reports of isolated cases or of a few cases do not usually include the views of the writer on the modus operandi of the treatment.

Sträussler and Koskinas, who made a comprehensive report on 38 cases, particularly emphasized the fact that they found a predominance of lymphocytes in the perivascular infiltrations. Two cases which died during the treatment showed miliary gummata. Sträussler and Koskinas concluded that the effect of the malaria is to transform the parenchymatous type of lesion into the granulomatous one characteristic of tertiary syphilis.

Gurewitsch recorded 12 cases, and also found an increase in the number of lymphocytes in the perivascular infiltrations. He considered that after malarial treatment the vascular changes are more characteristic of cerebral syphilis than of general paralysis, except in the basal ganglia, where there remains a predominance of the paretic process. Gurewitsch found the glial nodules described by Dürck in pernicious malaria present in a number of his cases which were treated by tertian malaria. The meningitis, which Gurewitsch observed in many cases, he took to be a malarial lesion. Miliary gummata were found in one case and inflammatory foci in another.

Kirschbaum, who reported 22 cases, considered that in the early febrile stage severe lymphocytic infiltration occurred, but that in patients who died later than a month after treatment the infiltrative reactions diminished and the parenchymatous changes were less severe. He found miliary gummata in two cases.

Lehoczky could not satisfy himself that any exacerbation of the inflammatory process took place during the early stages of malarial treatment. In his cases he described a definite diminution of perivascular infiltration as contrasted with untreated cases.

Wilson, who studied 45 cases in Jakob's laboratory, was of the opinion that there is a definite exacerbation of all the inflammatory processes with an increased production of microglia and a lymphocytic exudate within the first month to six weeks after treatment. If the patient survives this period, diminution in the exudate occurs and there is a gradual disappearance of the newly formed microglia. According to Wilson, the cortex even assumes a more normal lamination. A recrudescence of the paralytic process may occur any time after six months, and in these cases a more focal distribution of the inflammatory reaction was found. Miliary gummata were common in these cases,

and in five cases out of six spirochætes were found. Wilson was able to find spirochætes in only one out of twenty-nine cases dying within six months after treatment. The presence of miliary gummata would appear from these figures to favour the finding of spirochætes. This is contrary to the generally accepted view that spirochætes are very rarely present in the region of gummatous lesions in the brain or in the viscera. Wilson did not put forward a definite hypothesis in regard to the way in which malaria acts, though he suggested that altered permeability of the blood-vessels was in some way responsible. He was of the opinion, however, that the chief effect of malarial therapy was the destruction of most, if not of all, of the spirochætes in the cortex.

Geary, whose contribution to the Mott Memorial Volumes contained his experiences of the effect of malarial treatment on the histopathology of general paralysis, recorded 16 cases. In 10 cases which showed definite diminution of the pathological process, the minimum time which elapsed between treatment and death was three months, the maximum two and a half years. Of 6 cases which showed no improvement pathologically, 4 died within a month of treatment. The pathological improvement consisted mainly in a diminution of the perivascular infiltrations. Spirochætes were found in one case only, a congenital one dying eighteen months after treatment. In those cases which died within a month after treatment a lymphocytic reaction was noticed. Geary mentioned that in many cases perivascular infiltration in the cortex had subsided completely, whilst the vessels in the basal ganglia and mid-brain were still surrounded by many cells.

Ferraro also stressed the fact that the effect of the malarial treatment is on the inflammatory exudate. He reported twenty-nine cases and was the first worker on the subject of malarial treatment to compare the changes which malaria may produce in a normal brain with those changes which occur in the paretic brain after therapeutic malaria. The only lesion which Ferraro considered might be due to malaria in paretic cases was swelling of the endothelial lining of blood-vessels, not a typical syphilitic endarteritis, and acute degenerative changes in a few nerve-cells. He was unable to find Dürck's perivascular glial nodules which Gurewitsch observed in his paretic cases. Ferraro found that there was no aggravation of the paretic process during the early stages of treatment. In any case this would be difficult to substantiate as the intensity of the inflammatory changes varies from case to case, and it is obviously impossible to estimate the intensity of the process before treatment. In his cases the perivascular infiltrations did not become

totally lymphocytic ; where the exudate was greatly reduced the number of plasma cells was proportionately reduced. In many cases dying early in the treatment the infiltrations were very slight. Ferraro could not agree with Sträussler and Koskinas and Gerstmann that the essential feature of the malarial treatment is the transformation of the pathological process into the relatively benign gummatous type. He found inflammatory foci which did not present the appearance of miliary gummata in only two cases and in both of these death occurred too early in the treatment for the foci to have been formed during treatment. Ferraro holds the view that as the malaria kills the spirochætes the inflammatory exudate is absorbed because it is no longer needed. The other mesodermal reaction, that of the microglia, also diminishes in course of time, but the ectodermal processes are practically unaffected and there is no true reconstruction of cortical lamination. Ferraro's findings and conclusions have been given at some length because they accord in the main with my own.

Freeman also relied on the presence or absence of the perivascular exudate as evidence of the activity or quiescence of the paretic process. He also accepted destruction of the spirochætes in the brain as the starting point of pathological improvement, and offered the following suggestions as to the manner in which this destruction might take place : the spirochætes might be destroyed by the high temperature to which they were subjected during the rigors ; the microglial cells might become actively phagocytic and destroy the spirochætes ; or at the height of the fever when the nervous tissues were swollen and œdematous (as Kubie has shown occurs at very high temperatures), the spirochætes might be carried into the subarachnoid space by the current of fluid flowing along the courses of the perivascular channels. The main argument against the last possibility is that spirochætes have very rarely been found in the pia-arachnoid in general paralysis. It is much more probable that the spirochætes are destroyed by heat as good results have been obtained clinically from non-infective thermo-therapy.

In Freeman's opinion there may be actual reconstruction of cortical lamination in favourable cases after treatment, although the number of ganglion cells is reduced. But he also admitted that the process of degeneration of nerve-cells might be arrested at a time when atrophy of the cortex had not progressed to a marked degree. In view of the fact that manifestations of syphilis elsewhere in the body were more pronounced in successfully treated cases, that is, in cases dying more than two months after malarial treatment, without signs of an active

syphilitic process in the nervous system, Freeman came to the conclusion that the treatment did not kill all spirochætes, but merely suppressed their activity in the nervous system. This observation, that the lesions outside the nervous system are more frequent and more severe in cases successfully treated by malaria, has also been made by others. Schultze recorded cases of gummata of the skin of the thigh during remissions following malarial treatment. Wagner v. Jauregg reported cases of syphilitic joint disease, and Kirchbaum observed a case in which a gumma of the palate developed during a remission. Dr. W. J. Adie has kindly permitted me to quote a similar case which was under his care, that of a woman who developed gummatous ulceration and subsequent perforation of the soft palate during a remission following malarial treatment. The disappearance of the spirochætes from the brain appears, therefore, to be associated with an increase of their activity in other parts of the body after a certain time has elapsed. It would be valueless to speculate on the cause of this heightened activity in the absence of further pathological reports on both cerebral and visceral lesions.

Jakob regarded the diminution in perivascular exudate and inhibition of fresh neuroglial proliferation as the signs of pathological improvement in treated cases. He did not consider that any reconstruction of cortical laminæ could take place. Although several years ago Jakob was inclined to the view of Sträussler and Koskinas that the effect of malaria was to substitute a "benign" gummatous process for the "malignant" parenchymatous lesion, lately he has formulated his opinion thus: "Im allgemeinen lässt sich das Gesetz aufstellen, dass wir durch die Infectionsbehandlung häufiger und gesetzmässiger eine benigne Umwandlung des Krankheitsprozesses bewirken, wie sie—seltener—auch spontan in allen ihren Variationen zur Beobachtung kommen kann." ("Normale und pathologische Anatomie und Histologie des Grosshirns," Bd. II, p. 738.)

From my series of twenty-four cases treated by malaria I can confirm Ferraro's statement that there is no constant increase in the amount of perivascular infiltration during the first month after malarial treatment. Not one of the cases showed as much infiltration as the three untreated cases which died in or soon after a seizure. The case which showed most perivascular infiltration in the cortex was No. 28, the patient who had had five malarial inoculations and who died twenty months later immediately after a seizure. Slight perivascular infiltration was the rule, though in two instances it was completely absent, in cases which

succumbed twenty-six and thirty-one days after treatment. My cases differed from those of Freeman in that the perivascular cuffing was greater in his cases in the superficial layers of the cortex; in mine the heavier infiltration was always in the deeper layers of the grey matter and not infrequently, whilst there was little infiltration even in the deeper layers of the grey matter, the vessels in the white matter were heavily infiltrated. This was especially noticeable in Cases 5, 6, 8 and 15. There was very little perivascular infiltration in the cortex of Case 27, a congenital paralytic who died ten months after treatment, and in Case 26, in which death occurred two and a half months after treatment.

The microglial reaction appeared to bear no relation to the length of time the patient survived treatment. The congenital case showed as much as any which succumbed a few weeks after treatment.

Degeneration and loss of nerve-cells was greater in the congenital case and in Cases 4 and 21, in which there was no mesodermal reaction and to which reference has already been made. In general the cases did not exhibit gross disturbances of cortical architecture, and loss of nerve-cells, though usually evident, was not conspicuous.

The lesions in the basal ganglia merit special consideration, as in this country more attention has been focused in recent pathological reports on the cerebral cortex than on lower regions of the brain.

Jakob, whose experience of the pathology of neurosyphilis was unique, found the striatum regularly involved in general paralysis, both in cases treated with and without malaria. The thalamic nuclei usually showed degeneration and varying degrees of gliosis occurred in these ganglia. In his book on "Extra-pyramidal Diseases," Jakob gave his opinion that, in cases of paresis with striking disturbances of movement, the tremors as well as the components of the speech disturbances could be attributed to extension of the pathological process to the basal ganglia. Houlton, who found constant changes in the basal ganglia of four cases, also upheld this view; Kalnin made interesting observations on the distribution of the lesions in the basal ganglia and came to the conclusion that the disease might attack certain parts of the basal ganglia as severely as the cerebral cortex. The putamen was involved in every one of his thirty-five cases, whilst the pallidum escaped in all but four. In a large proportion of cases the cells of the thalamic nuclei were degenerated. Kalnin could not trace any relationship between the degree of tremor and the severity of the lesions in the basal ganglia, but all his cases had tremors during life. Steck studied the question of neuroglial proliferation in the basal ganglia and the distribution of the

lesions. Neuroglial overgrowth was constant in the putamen and caudate nucleus, whereas no proliferation occurred in the globus pallidus. The frequency with which lesions in the basal ganglia have been reported make it improbable that the specific lesions of general paralysis were responsible for the unusual choreiform disturbances which Fischer and Vogt described in their cases. Jakob is probably correct in correlating the regular involvement of the ganglia with the tremor, since we know that lesions in this region, such as those of chronic epidemic encephalitis, paralysis agitans, and Wilson's disease, are associated with involuntary movements and especially with tremor.

In my own series, lesions were present in the basal ganglia in sixteen out of twenty-two cases in which they were examined. I was unable to trace any connection between the severity of the lesions and the existence of tremor during life. Perivascular infiltration and the presence of rod-cells in large numbers were the most constant findings. These were particularly noted in the putamen and in the caudate nucleus. In agreement with Kalnin and Steck, I observed the relative freedom from involvement of the pallidum. Many cases showed neuroglial proliferation, and in several of the more long-standing cases degenerative changes were obvious in the nerve-cells of the thalamic nuclei. In Case 2, a very severe type, there was advanced degeneration of the nerve-cells in the thalamus, in the caudate, and in the nucleus of the oculo-motor nerve in the mid-brain. I was unable to satisfy myself that there was any difference in the severity of the lesions in the basal ganglia between those cases which had been treated by malaria and those which had not.

Perivascular cuffing was observed in the mid-brain, especially in the vicinity of the ventricle, in ten cases out of the nineteen in which it was examined. The exudate was not so intense in any of these cases as it was in the basal ganglia. In the congenital case only the medulla was available for section, but in the region of the fourth ventricle slight perivascular infiltration was present. The character of the infiltrations was predominantly lymphocytic in most cases, both in the basal ganglia and in the mid-brain, though a few plasma cells could be found in practically every case, and in some cases, notably in Case 2, in which they extended beyond the bounds of the perivascular spaces, plasma cells formed the chief constituent of the infiltration. Again, I was unable to determine any difference between malarial and non-malarial treated cases in this respect.

Conclusion.—My observations as regards the effects of malarial

treatment agree with those of Ferraro; destruction of spirochætes constitutes the starting point for the recession of the inflammatory exudate; there is no initial increase in mesodermal reaction, and the ectodermal lesions persist.

The Occurrence of Spirochætes in Cerebral Syphilitic Lesions.

Since 1913, when Noguchi announced his discovery of the *Spirochæta pallida* in the cerebral cortex of general paralytics, numerous workers have devoted much time to the problems of determining the distribution of spirochætes in the brain and their relationship to the tissues. Between 1913 and 1917, the difficulty of finding spirochætes in nervous tissues was further enhanced by the technical difficulty, which Noguchi himself encountered, of differentiating spirochætes from wavy nerve-fibres which also had an affinity for silver salts. Noguchi found spirochætes in roughly 25 per cent. of his cases (200). They were confined to the grey matter of the cortex and occurred in all layers of the cortex except the outer layer. No spirochætes were seen in the meninges or in relationship to blood-vessels or nerve-cells. Foster and Tomasczewski in 1914 reported a series of cases with positive results in 44 per cent.

Marie, Levaditi and Bankowski could find spirochætes in only 10 per cent. of cases by Levaditi's method. These authors found the organisms in close relationship to the walls of the smaller blood-vessels in the cortex. Marcus found spirochætes inside plasma cells in the frontal cortex, though he was unable to detect any in relationship to nerve-cells; one spirochæte was seen in the adventitia of a small capillary.

McIntosh and Fildes, who in 1914 reported the results of their examination for spirochætes in seven cases of general paralysis, first examined pieces of fresh brain by dark-ground illumination, and then fixed and stained the pieces by Noguchi's method. Spirochætes were detected in six cases by dark-ground illumination, but in only three were spirochætes seen on section. The organisms were found only in the grey matter and no relationship of them to blood-vessels or nerve-cells could be determined. One spirochæte was seen in the pia mater over the vertex, a situation of great rarity, as Levaditi and Jahnel have only once found spirochætes there. The cases from which McIntosh and Fildes derived their material were all recent and had shown acute manifestations of the disease before death.

The publication in 1917 of Jahnel's method for demonstrating spirochætes in nervous tissue gave a strong impetus to research on this subject as the method allows of a ready distinction between spirochætes, which stain an intense black, and nerve-fibres, which appear light yellow in colour.

Jahnel himself has fully investigated the question of the occurrence of spirochætes in the nervous system and many of his observations are of great value, especially in relation to the question of the occurrence of spirochætes in certain cases of general paralysis and after malarial treatment. In his article, published in 1918, Jahnel first described the three types of distribution of spirochætes which may be found in the nervous system; the diffuse type in which spirochætes are scattered irregularly through the tissues; the "swarm" type in which aggregations of spirochætes, sometimes large enough to be visible to the naked eye, occur in localized areas; and the vascular type, the rarest, in which the walls of blood-vessels are surrounded and infiltrated with spirochætes. Jahnel was of the opinion that the spirochætes, which may very occcasionally be found in the lumina of vessels, reach there after death. Usually only one type of distribution is found in one brain.

Spirochætes are most commonly detected in the grey matter of the anterior part of the frontal lobe, though there is hardly a region of the brain in which their presence has not been recorded. Grant and Kirkland, who examined fifty cases of general paralysis and found spirochætes present in 62·5 per cent., maintained that if spirochætes were not present in sections from the anterior part of the frontal lobes they would certainly not be found in any other part of the brain. They met with spirochætes in the thalamus, the corpora quadrigemina, the cerebellum and the grey matter of the aqueduct of Sylvius, but not in the pia mater. Jahnel also found spirochætes in the basal ganglia, in the neighbourhood of the aqueduct of Sylvius, and in all layers of the cerebellar cortex. Sioli, Dieterle, and Pacheco E. Silva also found them in the cerebellum and in the basal ganglia. Jahnel mentioned the rarity of spirochætes in the mid-brain in the region of the oculo-motor nuclei and discussed their possible relation to the production of the Argyll Robertson pupil, but decided it was not possible to draw any conclusion from their presence. Igesheimer has reported two cases of general paralysis in which he found spirochætes in the optic chiasma and optic tract. Aars, in a careful study of thirteen cases of general paralysis and three cases of cerebral syphilis, was unable to detect spirochætes in the meninges, pons, cerebellum or medulla, although they were found in the cerebral cortex in nine cases.

Many more examples might be cited, but sufficient evidence has been given to substantiate the statement that spirochætes may be found anywhere in the brain. Failure to find them either in their most usual habitat or in less common situations, depends not so much on faulty technique or lack of patience on the part of the observer as on selection of the wrong type of case.

The experience of most workers has been that the cases in which spirochætes are likely to be present are those which presented the features of euphoria and grandiose delusions during life. Jahnel, Hauptmann, Sioli, Smyth, Aars, all agree on this point.

The cases which have died either in or just after a seizure have provoked a good deal of discussion. Some authors, Jakob and Jahnel for example, maintain that in these cases the death of the patient is due to a liberation of the toxins from innumerable spirochætes which have suddenly invaded the cerebral tissues, and that spirochætes should therefore be readily found in large numbers; others, as Hauptmann and Ehrlich, consider that the fatal convulsive attack is analogous to anaphylactic shock, and is due to the rapid absorption of toxins produced in the process of destruction of many spirochætes by antibodies. Therefore spirochætes would be few or absent in such cases.

Jahnel agrees that if life is prolonged for a few days after such an attack the antibodies called out may have time to destroy the spirochætes, and so none may be found in the brain, but he claims that the presence of the spirochætes and not the reaction against them provokes the convulsive attacks. Grant and Kirkland found spirochætes present in only 21 per cent. of cases in which seizures had occurred, whilst 50 per cent. of their negative cases had died in seizures. Wilson found spirochætes in one case out of six which died in acute attacks.

My own cases, though of interest, are not sufficient in number to allow of any expression of opinion on this point. Of the twenty-eight cases which I examined for spirochætes, twenty-four had been treated by malaria, and only one of these had survived longer than two months. The disappearance of spirochætes from the brain for several months after malarial therapy has been stressed by many. Wilson found spirochætes present in cases which died fourteen days after treatment, and then only in cases which succumbed at a later date than six months from the malarial inoculation. In Geary's series of sixteen cases treated with malaria, spirochætes were found only in one case of juvenile general paralysis which died eighteen months after treatment. Kirchbaum, Schilling, Bratz and Bielschowsky, Jossman and Steenaerts, all reported failure to find spirochætes in cases treated by malaria.

It was not surprising, therefore, that I was able to find spirochætes in only two of the cases which had been treated by malaria. One of these (Case 13) died sixteen days after the inoculation—after having had five rigors. The patient did not die during a rigor. A very few spirochætes were present in the deeper layers of the frontal cortex and those were short forms with bulbous ends and obviously degenerate. Seldom more than two or three could be demonstrated in a section. None could be found in the mid-brain or floor of the fourth ventricle.

The other case (Case 28) was a striking contrast to the last. Malarial inoculations had been given on five separate occasions, the last occasion two years before death. Intensive tryparsamide and mercurial treatment had been given until two months before death, which followed a seizure. Enormous numbers of spirochætes were present in all layers of the frontal cortex, though the numbers varied in blocks of tissue. (The pieces of brain were sent to me already cut into small pieces, and it was not possible therefore to identify the exact region of the frontal cortex with which I was dealing). Although in many sections only a diffuse arrangement could be determined, in a few definite aggregations of forty to fifty spirochætes were seen. These aggregations were hardly worthy of the term "swarm" as the spirochætes were not packed closely together, though they were sufficiently localized to form aggregations. Many spirochætes were also observed in the walls of blood-vessels and one was found lying in the lumen of a vessel. Thus in one brain there were the three types of distribution, which is, according to Jahnel, a most uncommon occurrence. Haupmann holds the view that the types of distribution of spirochætes are transitory and are constantly changing; any one, or all three types, may therefore be encountered in the same brain. The findings in this case certainly suggest that this view is correct. I was unable to find spirochætes in the ependymal granulations in the floor of the fourth ventricle. (The medulla was the only other part of the brain available for section.)

The only other positive cases were two which had not been treated by malaria. Both of these died after seizures; one (Case 1) three hours after the seizure, the other (Case 2) two days later. In both these cases spirochætes were extremely scanty. Six blocks of tissue from the frontal cortex were searched without success in Case 2; in the seventh block four sections were obtained which each contained two or three spirochætes. Most of those present were of the short type and showed early degenerative changes, as the formation of bulbous ends, though a few long forms were seen.

I could not find any atypical "rolled up" or ring-like forms such as Jahnel has described in any of my cases. In Case 1, which succumbed three hours after a seizure, the spirochætes were of the long type and none had bulbous ends. The mid-brain and medulla were searched for spirochætes without success in this case.

Of the other two cases not treated by malaria, one died after a seizure, but in neither could I find spirochætes.

My results, therefore, conform to those obtained by most workers in that in at least 50 per cent. of cases not treated by malaria spirochætes can be found, whilst it is extremely difficult to find them in treated cases within six months from the date of treatment; my results, two positive out of twenty-four, give a percentage of 8·4.

With the exception of Sioli, who found a rolled-up spirochæte in a a cell infiltrating a blood-vessel, and Marcus, who found one inside a plasma cell, observers have been practically unanimous that spirochætes in the brain do not penetrate either nerve-cells or infiltrating cells; nor do they occur in the subcortical white matter. My observations agree that the nerve-cells and mesodermal cells apparently form impenetrable barriers to the passage of the spirochæte, as I was unable to find any intracellular spirochætes, nor could I demonstrate any in the white matter. My failure to find them in any other part of the brain except the frontal cortex is difficult to explain, as control material was nearly always prepared at the same time and likely parts of the brain (mainly mid-brain and floor of fourth ventricle) were chosen for section.

Extracerebral Pathology of Neurosyphilis.

The association of syphilitic aortitis with neurosyphilis has long been known clinically, and it is found pathologically in a very large percentage of cases. The possible significance of this association will be discussed later, but it is essential to point out that although syphilitic lesions co-exist in the aorta and in the nervous system, mild degrees of syphilitic aortitis are an exceedingly common finding in cases in which no other syphilitic lesion can be detected. McIntosh and Fildes discovered a definite mesaortitis in a very high proportion of cases at 314 post-mortems taken at random, this in many cases being the sole demonstrable syphilitic lesion. The aorta would, therefore, appear to be the favourite habitat of the *Spirochæta pallida*.

The clinical evidence of the association of aortic and nervous syphilis is much less frequent than is the pathological. Schlesinger, who commented upon the lack of symptoms which many patients with aortic

and nervous syphilis present, found clinically aortitis in 19·2 per cent. of his cases. He stressed the relatively benign character of aortic disease when associated with syphilis of the nervous system, the absence of cardiac pain being a special feature. Schlesinger suggested that destruction of the nerves in the peri-adventitial nerve plexuses might account for the absence of this most characteristic feature of aortic disease, but this suggestion cannot be accepted because, before destruction of nervous tissue occurs, signs of irritation would appear and pain would, therefore, be a prominent early feature. The observations of Schlesinger were not confirmed by those of Carey Coombs, who found that cardiac pain was present in over half his cases of cardiac and aortic syphilis. He found evidence of syphilis of the nervous system in about 13 per cent. of these cases, 10 per cent. showing the clinical manifestations of tabes dorsalis, and 3 per cent. those of general paralysis. Deneke detected clinical evidence of mesaortitis in 40 per cent. of patients with general paralysis, whilst Frisch was able to demonstrate the aortic condition in only 29 per cent. of cases of this disease.

On the pathological side, Straub found aortic disease in 80 per cent. of cases of general paralysis and Daniels and Arndt in 75 per cent. Jakob, in a series of 890 general paralytics, found aortic lesions present macroscopically in 60 per cent. of cases; but a definite macroscopic syphilitic mesoaortitis only in 40 per cent. Microscopically, however, 70 per cent. of aortas from cases of general paralysis were proved to have the typical lesions of syphilitic aortitis. Jakob referred to the two types of lesion in the aorta which Benda described, one showing miliary gummata in the media with areas of necrosis and giant-cell formation, and the more common type in which infiltration with plasma cells and lymphocytes occurs in the media and adventitia, especially in relation to the vasa vasorum. Jakob came to the conclusion that the gummatous type was exceeding rare as he encountered it very seldom in his series of cases.

Freeman did not give exact figures for the proportion of aortitis to general paralysis which he found in his series of 71 cases, but out of 23 cases which died within two months of malarial treatment, 10 had a definite macroscopic aortitis and 6 had syphilitic changes in the myocardium.

The demonstration of the *S. pallida* in sections from aortas with evidence of gross macroscopic syphilitic mesaortitis is simple in cases in which this lesion has resulted in the death of the patient. Warthin, to whom we owe so much of our practical knowledge con-

cerning the presence of the spirochæte in the viscera, has described both typical and atypical spirochætes in a very high percentage of such cases. But in cases in which a concomitant lesion in the nervous system has been the cause of death spirochætes have only rarely been demonstrated in the aorta. Jahnel found them once, in a case of general paralysis. Grant and Kirkland found them twice in cases of general paralysis; in one case, which had been treated by malaria, no spirochætes were found in the brain, in the other spirochætes were present in the cortex and medulla of the suprarenals as well as in the cerebral cortex. As far as I have been able to ascertain, spirochætes have not yet been demonstrated in the aorta in tabes. Jahnel in discussing the question of their occurrence in the aorta in general paralysis emphasized the fact that in his opinion although ring-like, "rolled-up" or other grossly atypical forms might be present in the aorta it was wise to accept these appearances as true spirochætes only if typical spiral forms could also be seen.

Syphilitic lesions of organs other than the aorta would appear to be rare in general paralysis and tabes. In his series of 890 cases of general paralysis. Jakob observed cirrhosis of the liver only once, and was unable to satisfy himself that lesions which occurred in other organs were definitely syphilitic.

Freeman, on the other hand, found a high proportion of cases of cirrhosis of the liver in his series of seventy-one general paralytics; thirteen of these had definite cirrhotic changes, a percentage of 18. Freeman remarked that the cirrhotic lesions were more pronounced in cases which had been successfully treated by malaria than in those in which the inoculations had failed, but he could not attribute the cirrhosis to possible harmful effects of the malaria as the disease in the liver was invariably of long standing. It is difficult indeed to explain the wide differences between the findings of Jakob and of Freeman. The possibility of a national susceptibility to visceral syphilis must be considered, especially in the light of Warthin's work on latent syphilis. Comparison with German figures of the frequency of latent syphilitic lesions of the viscera would prove instructive.

In my series of 28 cases of general paralysis, the aorta was examined macroscopically in 23 and microscopically in 11 cases, but in three cases in which no microscopic examination was made the naked-eye appearance of the aorta was typical of syphilitic aortitis. Microscopically all except one case showed definite cellular infiltration of the vasa vasorum and of the media with small lymphocytes and plasma cells, the

characteristic picture of syphilitic aortitis. Thus aortitis was present in 13 cases out of 23, or in 56·5 per cent. This proportion would have been considerably higher if all the aortas had been examined microscopically, for only 5 of the 11 which were sectioned had shown the naked-eye appearances of syphilitic aortitis; the others had shown varying degrees of atheroma, not obviously of a syphilitic nature. Clinical signs of aortic disease had been found in four cases (16 per cent.) of 25 in which a note was made on the condition of the cardiovascular system. Only one of the six tabetic cases, or 16·6 per cent., gave clinical evidence of aortic disease.

The aorta was examined macroscopically in six cases of pure tabes and in two of those there was a definite aortitis. All the others showed moderate to severe degrees of atheroma. Unfortunately only one of those was available for section and in this case the lesions were microscopically typical of syphilitic aortitis. The proportion of cases of tabes in which a syphilitic lesion could be demonstrated was therefore 50 per cent.

All the aortas sectioned were stained for spirochætes, many by Jahnel's method as well as by Levaditi's, but I was unable to detect spirochætes in any one of them.

The rarity with which spirochætes have been found in the aorta in lesions associated with nervous syphilis suggests that it is not the presence of the spirochæte itself, but that of its toxins, which is responsible for the lesions both in the aorta and in the nervous system. In a study on the histopathology of the tabes, I tentatively put forward the suggestion that the aorta might be a focus harbouring spirochætes which could exert their toxic effects on the cord and produce degeneration of the posterior columns in the same way that this degeneration may be produced by bacterial toxins passing along the afferent nerves by the perineural lymphatics. Since that study was written, Carey Coombs in his Lumleian Lectures has expressed the view that the lesions in syphilitic aortitis are due to toxins from the spirochætes which lie outside the aorta, in the mediastinal lymph glands, whence they are able to pour their toxins into lymphatic channels and can thus affect both the aorta and the spinal cords. This hypothesis accords with the parallelism between aortic syphilis and parenchymatous spinal syphilis which Carey Coombs described, and is one which requires to be fully investigated.

I could find no syphilitic lesions in other viscera except in one case, that of a congenital general paralytic, in which there was microscopically an early monolobular cirrhosis of the liver. In two other cases at post-

mortem examination the liver appeared to present the features of an early cirrhosis, but on section the only lesion found was an intense fatty degeneration.

The Age Factor in the Histopathology of Parenchymatous Cerebral Syphilis.

In order to compare the histological lesions of general paralysis in childhood, adult life and old age, Cases 27, 18 and 13 were selected. Case 27 was one of congenital paralysis in a child aged 8 years and 10 months, who survived malarial treatment for ten months; Case 18 was that of an adult, aged 32, whose symptoms began only six months before admission to hospital and who died twenty-four days after malarial inoculation; Case 13 was that of a man of 62, with a history of symptoms for two years, who died sixteen days after inoculation, having had five rigors.

The only conspicuous difference between the three cases was the greater loss of nerve-cells from the cortex of the child. No cells could be seen degenerating but there had obviously been a gross "falling out" of nerve-cells. The vessels in the cortex of the congenital case were relatively much thicker than those in the adult cases.

The case of the elderly man was singularly uninstructive since it presented none of the histological features to which Critchley has called attention. The number of microglial cells was certainly larger than in many cases, but typical rod-cells formed a large proportion of the microglia and this form is not associated with senile changes. No Alzheimer's tangles or other evidence of metabolic disturbances of nerve-cells could be observed. Several areas of the cortex were stained by Bielschowsky's method in an endeavour to demonstrate senile plaques, but without success. It was surprising to find that in the brain of an elderly man with a psychosis those plaques were absent; their specificity for senile dementia would appear to be almost absolute. The adult case, No. 18, was in no way remarkable.

On the basis of those three cases it is obviously impossible to base any opinion on differences in tissue reactions in cases of general paralysis at different periods of life. This study is being continued.

General Conclusions.

Three discoveries during the last thirty years, those of Wassermann, Ehrlich and Wagner v. Jauregg have resulted in an entirely new conception of syphilis both clinically and pathologically. This is parti-

cularly true of neurosyphilis, which before the days of the Wassermann reaction, organic arsenical compounds and therapeutic malaria was a disease difficult to diagnose and hopeless to treat. The Wassermann reaction made the diagnosis of neurosyphilis simple ; the new therapeutic measures not only altered the clinical course ot the disease but modified the pathological nature of the disease process.

All pathologists are agreed that whereas before the introduction of organic arsenical compounds tertiary manifestations of syphilis, especially in the nervous system, were common, nowadays the occurrence of a gumma in the brain, spinal cord or viscera is a great rarity. On the other hand the incidence of syphilitic disease of nervous tissue itself has become more frequent, particularly in those patients who have shown few or no secondary symptoms, and who have been actively treated in the early stages of the disease.

It is generally admitted that the strong reaction of the mesodermal tissues which gives rise to the tertiary phenomena is due to a vaccination of the patient in the secondary stage by the dissemination of spirochætes and their toxins throughout the body. The suggestion has been made, which is probably correct, that if this vaccination does not occur there is a poor reaction of the mesodermal tissues and spirochætes are enabled to flourish in the brain ; they are not walled off by fibrous tissue. If the secondary phenomena are aborted by early active treatment no immunity is produced, and the so-called parenchymatous form of neurosyphilis results. Many affirm that the effect of malaria on the disease process in general paralysis is to transform the reaction of the parenchymatous type of lesion into that of the gummatous tertiary type. Others deny this and state that there is no evidence of a mesodermal reaction. Certain facts seem to suggest a possible interpretation of contradictory results.

The starting point of any healing process must be destruction of spirochætes. Experimental evidence by Jahnel and Levaditi is in favour of this destruction being caused by the intermittent high temperature to which they are subjected during the malarial paroxysms. Jahnel and Levaditi have both shown that in rabbits inoculated with the *Spirochæta pallida* production of high, and especially intermittent high, temperatures causes a widespread destruction of spirochætes. It is possible that toxins liberated by the sudden killing off of large numbers of spirochætes in the brain during the malarial paroxysms may produce some local or general vaccination as in the secondary stage of syphilis and thereby cause a tendency to a gummatous or mesodermal reaction.

The occurrence of the reaction will be determined by two factors: the rate at which immunity develops in the patient, and the survival of spirochætes in the brain or in the lesions of latent syphilis which Warthin has shown are so frequently present.

There is a certain amount of evidence to support this contention. In large series of cases, including those of Ferraro and my own, a diminution in the inflammatory exudate has been observed in the first two months after malarial treatment. This phase corresponds to the destruction of spirochætes. The second phase is that of a remission. During the remission immunity develops in the patient. The appearance of tertiary lesions in the skin, joints and viscera during remissions which numerous workers have observed results from this immunity reaction in the same way as gummata in the tertiary stage are consequent upon vaccination in the secondary stage of the disease. Further, Wilson found in cases which relapsed after a definite remission that there were large numbers of miliary gummata in the brain, and spirochætes in five cases out of six. This formation of gummata in the brain is a special expression of a potentially general mesodermal reaction. The phase of immunity will determine when it occurs. Whether the lesions produced in this way are as amenable to treatment as the tertiary lesions following the secondary stage we have as yet no means of judging. As Monrad-Krohn wrote: "The killing off of no matter how many spirochætes does not recreate one single neurone that has once been destroyed"; a truism which explains the frequent discrepancy between clinical and pathological improvement in malarial treated cases of general paralysis.

Summary.

(1) A series of cases of general paralysis and tabes dorsalis has been studied with special reference to certain aspects of the pathology.

(2) Cases illustrating mild and severe types of lesion in general paralysis and the modifications found after malarial therapy have been recorded.

(3) The constant presence of lesions in the basal ganglia in general paralysis identical with, and often as severe as, those in the cerebral cortex has been emphasized, and the relationship of these lesions to the characteristic tremor has been discussed.

(4) The histological diagnosis of general paralysis has been considered, and the conclusion has been reached that except for the demonstration of spirochætes in the brain the most reliable and certainly

the quickest method by which general paralysis can be diagnosed histologically is by means of the Prussian-blue reaction in the microglial cells. This method is valuable because it is applicable to material after prolonged fixation.

(5) The frequent occurrence of syphilitic lesions, which are often symptomless, in the aorta is contrasted with the rarity of other visceral lesions in general paralysis and tabes dorsalis. The extreme difficulty of finding spirochætes in the aorta in the aortitis which occurs in association with these two forms of syphilis of the nervous system strongly suggests that the presence of the spirochæte is not essential for the development of the aortic lesion; the question of the existence of spirochætal toxins is raised.

(6) The influence of age on the morbid process in general paralysis has been discussed. Degeneration and disappearance of nerve-cells appeared to be the feature of the congenital case; no exceptional lesions could be demonstrated in the brains of elderly patients.

(7) The occurrence, distribution and localization of spirochætes in the brain in general paralysis have been considered, especially in relation to malarial therapy and its mode of action.

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ACUTE PERIVASCULAR MYELINOCLASIS ("ACUTE DISSEMINATED ENCEPHALOMYELITIS") IN SMALLPOX.

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"The variolous process possesses, in a marked degree, the power to awaken latent predispositions to nervous disease, as well as to independently disorder function and create anatomical alterations in the various nervous structures of the body." (ALDRICH, 1904.)

INTRODUCTION.

THE encephalomyelitis occurring since 1922 as a sequel to vaccination has evoked great interest and much speculation. With a more or less characteristic symptomatology and a highly characteristic histology, to escape observation the disease, though certainly present in the past, cannot ever before have occurred with its recent frequency. Various observers, according to their tendency to broad outlines or to minute classification, have stressed its resemblance, or lack of resemblance, to certain other demyelinating neuropathies of unknown ætiology occurring independently of the exanthemata. All questions of ætiology must take into account the fact that encephalomyelitis of precisely similar type has followed measles, antirabic treatment, &c. Although during the last few years cases suffering from a mild form of smallpox have been relatively numerous, during the present decade only two examples of encephalomyelitis following variola have been described. Our object in this paper is to show that smallpox, probably no less than vaccinia, is a powerful excitant, direct or indirect, of the type of nervous disease to which, when following vaccination, the title "post-vaccinal encephalitis" has been appended.

NOMENCLATURE.

The term "acute disseminated encephalomyelitis," commonly used in reference to these cases, contains nothing to indicate the specific nature of the lesions by which the disease is differentiated from others

to which the same title has been applied. In the absence of definite knowledge of their ætiology, it is by no means certain that the lesions are primarily inflammatory in nature. In all the encephalitides attributable with certainty to a virus, the primary attack is on the grey matter; this is true also of those due to the majority of bacterial and inorganic toxins. Moreover, since the disease under discussion, excited by a rather heterogeneous group of factors including vaccinia, measles and antirabic inoculation, is in essentials always the same, it is clear that we are dealing with a single clinical and pathological entity; this should be recognized by the use of a single comprehensive term embracing all the cases, whatever their exciting cause. We propose, therefore, to use in this paper the term "acute perivascular myelinoclasis" as indicating its essential features, without bias towards one or other theory of its causation. In using the adjective "perivascular," we do not necessarily imply that the causative agent is blood-borne, for the vessel wall contains the Virchow-Robin space, a direct extension of the subarachnoid cavity; zones of demyelination are also found at the periphery of the cord and beneath the ependyma of the lateral ventricles. We propose the term "myelinoclasis" because the constant and essential feature of the malady, and the histological criterion of its existence, is destruction of the myelin sheaths over a zone around the vessels; because damage to the axis-cylinders, though always present in some degree, is relatively less severe; and because inflammatory phenomena, as perivascular infiltration with lymphocytes, &c., vary greatly in intensity from case to case, and may conceivably be excited by the irritating products of myelin degeneration.

Literature and Statistics.

From an early period of the history of the disease, nervous symptoms have been recognized as complicating or following smallpox; early references are those of Clifton (1724), and Freind (1730). Apart from initial convulsions, delirium and mental changes due to the toxæmia of the disease, many affections of the nervous system have been recorded, but it is often difficult to pick out cases which may have been examples of the type described in this paper. Many cases recovered, and in those which succumbed post-mortem examination frequently failed to do more than differentiate purulent from non-purulent affections.

The frequency of nervous complications has been variously stated. MacCombie (1905) stated that in variola the nervous system is more often involved than in any other exanthem; Rundle (1929), on the other hand, has never seen these complications. Schamberg and Kolmer (1928)

observed eight instances of paralysis among about 3,000 cases of smallpox; of which five died and three recovered. The opinion of Aldrich (1904) has been quoted above, and that of Immermann (1902) is similar.

Among the records of 15,000 cases treated in the smallpox hospitals of the Metropolitan Asylums Board between January, 1893, and December, 1927, the writers found one case diagnosed as Landry's paralysis, the onset of which probably preceded the attack of smallpox; the one, recorded in this paper, of myelitis associated with optic neuritis; five of "meningitis"; eleven of "peripheral neuritis"; one of "paraplegia," and two of "paralysis."

Some of the nervous complications recorded in the literature have evidently been secondary or coincident, as the purulent meningitis of Wagner (1872), and the streptococcal meningitis and myelitis of Auché and Hobbs (1894). Damaschino (1871) described a case which was certainly poliomyelitis. The case of Oettinger and Marinesco (1895) might have been an example of the disease here described but for the authors' claim to have demonstrated micrococci in the infiltrating cells and in the nerve cells; other observers, e.g., Turnbull and McIntosh (1926), do not consider this evidence convincing.

The older writers recorded many cases where peculiar disturbances of speech occurred, either alone or combined with dysfunction of muscles supplied by the bulbar nerves, or with a paralytic or ataxic state. The relation of such conditions to disseminated sclerosis was often discussed. Gubler and Laborde (1871), Guttstadt (1872), Wohlrab (1872), Combemale (1892), and Aldrich (1904), described cases where partial or complete loss of speech alone occurred. In many of these symptoms commenced during the early or toxæmic stage of smallpox and disappeared quickly. Westphal (1872) described four cases in which disturbance of speech was associated with ataxia but with no loss of sensation; words were squeezed out with syllables spaced at equal intervals, and great difficulty was encountered in the pronunciation of certain letters. Whipham and Myers (1886) related similar cases of two women who emerged from the toxæmic stage of smallpox with weakness of the limbs, and with an utterance which was at first incoherent but which later assumed a jerky, squeezed-out character, giving the impression of great muscular effort, and which was apparently not associated with paralysis of tongue, throat or larynx. Difficulty in the pronunciation of certain words and letters is recorded in the first case. There were neither sensory nor sphincter disturbances, and intelligence once regained was acute. Whipham and Myers quote seven similar cases from the literature, in addition to those described by Westphal.

Aldrich (1904) published a number of cases of which two may be outlined. In the first, a boy aged 13 was found, on the twelfth day after appearance of the rash, in a stupid condition from which he could not be roused. For four or five days speech was slow and hesitating; aphasia then developed. When speech returned five weeks later it was slow, scanning and thick. When allowed to walk the patient was grossly ataxic. There was a marked change in his disposition. In the second case, delirium on the third day of the rash was followed by loss of sphincter control, loss of speech, difficulty in swallowing and quadriplegia. Speech returned after three weeks, but marked ataxia persisted for three months. Certain points in the history suggest superadded hysterical manifestations. Kleinberger (1913) and Sottas (1892) have described similar cases.

Spiller (1903) examined a woman observed by Schamberg, who during the initial stage of smallpox was stuporose, barely able to articulate, had difficulty in swallowing, and impairment of power in the arms and legs. Almost complete loss of power in the limbs followed, and later a gradual restoration of function. There was pronounced scanning speech.

There is also to be found in the literature a group of cases in which paralysis of the limbs occurred with or without paralysis of the bladder and rectum.

Leroy d'Étiolles (1856) mentions paraplegia during the incubation period of smallpox in a woman, aged 21; sensation was not affected. After the eruption appeared the palsy improved, but death occurred later. No lesions were found in the central nervous system. In another case complete paralysis and loss of sensation in the lower limbs came on when the rash was desiccating. There was paralysis of the bladder and rectum, and later the left arm was involved. No lesions were found in the nervous system.

In a patient recovered from an attack of confluent smallpox, Gubler and Laborde (1871) observed paralysis of the legs, at first complete but gradually improving over a period of three months.

Bernhardt (1871) and Guttstadt (1872) described a man, aged 28, who on the eighth day of smallpox complained of numbness in the right hand and weakness in the limbs. Loss of power in the right arm increased and the legs became paralysed. Incontinence of urine was present. Post-mortem, no lesions were found in the central nervous system.

Westphal (1874) published details of a man, aged 32, who on the

eleventh day of a smallpox rash was incontinent of urine. Next day there was retention of urine with paralysis of the left leg. On the thirteenth day both legs were affected and later incontinence of fæces was present. On the seventeenth day a sacral bed-sore developed; paralysis was complete but sensation was merely diminished. Cystitis and sepsis led to death four weeks after the onset of paralysis. Post-mortem, some softening of the cord with congestion of the grey matter was noted. Microscopically, the blood-vessels were dilated and invested with sheaths of granular corpuscles. Extensive infiltration with similar cells affected chiefly the grey matter; no changes were demonstrated in the nerve cells.

Westphal also described the case of a man, aged 22, who on the fourth day of the eruption could not move his legs and was incontinent of urine. His condition gradually improved but he later died from perityphlitis. Here the lumbar cord was most affected and the grey matter less than the white. There was but little destruction of ganglion cells. Westphal named the condition "disseminated myelitis."

Fiessinger (1898) reported the occurrence of acute myelitis as a complication of smallpox. Immermann (1902) stated that the cord is affected more frequently than the brain, and that paraplegia of rapid onset associated often with sphincter paralysis but without sensory loss may follow either mild or severe variola.

Spiller (1903) recorded two cases. During the third week of smallpox a woman, aged 19, developed inability to move her legs, impairment of sensation and incontinence of urine and fæces. Although partial restoration of power in the legs soon occurred, death followed the onset of severe diarrhœa about two months later. Post mortem, no changes were found, but examination was incomplete. In the second case, a man aged 36 lost power in the legs on the eighth day of the rash. Retention, and later incontinence, of urine and fæces was followed by diarrhœa terminating in death. Before death some recovery of power was noted in the legs. In the lumbar region, where lesions implicated chiefly the grey matter, the myelin sheaths had disappeared from the anterior horns while the degree of involvement of the nerve-cells was slight. In the mid-thoracic region both grey and white matter were affected. At the time he considered the case to be one of poliomyelitis, but he has since (1929) accepted it as one belonging to the group under discussion.

In Eichorst's case (1913), weakness of the legs with abolition of tendon and plantar reflexes suddenly developed on the eleventh day of

the rash. There was no loss of sensation. Urinary and fæcal incontinence were succeeded by retention of urine. No spread of the paralysis took place, but the man died three days later of urinary sepsis. At autopsy the nervous system appeared normal. Microscopically, however, the whole length of the cord was beset with hæmorrhagic and inflammatory foci most marked in the lumbar region. The white matter was most affected, and in the grey the nerve-cells were fairly well-preserved even when situated in a densely infiltrated zone. Foci of mononuclear cells lay in the nervous tissues in immediate relation to the blood-vessels and pial septa, and a round-cell infiltrate occupied the perivascular spaces. The illustrations suggest the type of lesion present in our own cases.

Of the two recorded instances of this disease occurring coincidently with the recent outbreak of post-vaccinal encephalitis, McIntosh and Scarff (1928) examined one. McIntosh (1928) described perivascular and extra-adventitial infiltration accompanied by demyelination around the blood-vessels.

The second was that of Troup and Hurst (1930). Here an unvaccinated man, aged 63, developed symptoms of myelitis on the twelfth day of the rash. Death from sepsis took place nearly one month later. The lesions, almost wholly confined to the cord, brain-stem and cerebellum, were such as are described in the present paper, except for those modifications due to their greater age. The writers studied the returns of the Registrar-General for the period 1925-1929 and concluded that in all probability during that time other undiagnosed cases had occurred.

Summary.—Among the nervous complications of variola, therefore, are recorded affections of the nervous system clinically unlike pyogenic infections or proved after death to be non-pyogenic. Disregarding the cases of initial convulsions, &c., due to the toxæmia of the disease, cases of peripheral neuritis, and cases of coincident or secondary infections, two clinical groups remain.

In the first the most prominent feature is a disturbance of speech remarkably similar in all instances. Following complete inability to speak, the power of utterance slowly returned but resulted at first only in unintelligible sounds. Later speech assumed a typical slow, monotonous form in which the words appeared to be "squeezed out" by great muscular effort, with the syllables equally spaced. Improvement was apt to be extremely slow. Most authors were at pains to draw a distinction between this and the typical "scanning" speech of dis-

seminated sclerosis, and also to stress the appearance of great muscular effort accompanying attempts to talk. In most cases these symptoms were evident early in the attack of smallpox as the patient recovered from the mental disturbances of the toxæmic stage. Owing to its favourable course the pathology of the condition remains obscure.

In the second group paralysis of the limbs, with or without sphincter disturbance, was the prominent feature, and a considerable number of the cases proved fatal; they approximated more closely in their symptomatology, in their temporal relation to the appearance of the exanthem and, as far as we can tell, in their histology, to those we describe.

Case Records.

The following records of eleven patients suffering from acute nervous symptoms in association with smallpox (nine of whom were under the personal observation of one of us—J. P. M.) are recorded here for the first time.[1] From a clinical point of view we divide the cases into two groups, and shall later discuss the relation, if any, existing between those in the second group and the typical examples of acute perivascular myelinoclasis forming the first group. The latter consists of seven patients: of these four, including a boy with concurrent vaccinia and variola, recovered more or less completely, while three died and were examined pathologically. The second group contains the remaining four patients, and includes one "borderline" or "abortive" case in which the symptoms were vague and transient; one intermediate between this and the definite cases; a patient in whom nervous symptoms predominated at the onset of the toxæmic stage of smallpox, and a case occurring in the year 1899 of an acute nervous disorder in the course of a severe attack of smallpox. This last case proved fatal, but pathological details are lacking.

Group I.

Case 1.—A. P., aged 10, an unvaccinated boy, had suffered previously from measles and whooping-cough. Initial symptoms of smallpox commenced on December 29, 1929. The eruption appeared on January 1, 1930, and on the 6th there was pain in the back and limbs. On 7th the patient was admitted to hospital with a late pustular eruption of modified smallpox, type six (less than a hundred lesions on the face); his temperature was 99·6° F. and his pulse-rate 100.

[1] For permission to publish clinical details of these cases, with the exception of Case 7, we are indebted to Dr. A. F. Cameron, Medical Superintendent of the L.C.C. Smallpox Hospitals.

On the evening of January 8 the boy was drowsy and listless and complained of pain in the back. On the morning of January 9 the child could be roused only with difficulty, and was resentful of interference. Retention of urine with overflow incontinence was present. The left pupil reacted to light, the right one did not. The patient could swallow but took fluids unwillingly. Tendon, plantar and abdominal reflexes could not be elicited. The arms were slightly rigid but could be moved freely; the legs were flaccid and voluntary movement was not possible. Kernig's sign and head retraction were present. The patient resented pin-prick on the right cheek only and appeared to be insensitive to strong compression of either tendo Achillis. Lumbar puncture gave a clear, colourless fluid. Urine, free from abnormal constituents, was obtained by catheterization. On January 10 there was little change. The right pupil now reacted to light. Tache cérébrale was obtained. The optic discs appeared normal. Lumbar puncture yielded a little blood-stained fluid on which the following report was issued.[1] "Cell count, 595 cells per c.mm. A large number of red cells present. Cultures, sterile. No tubercle bacilli found."

On January 11 the child could be roused to open his eyes and mouth more easily but could not be induced to speak. The left pupil was larger than the right; both reacted to light. Slight respiratory stertor was noticed. At night the temperature rose. Breathing became stertorous and at times cyanosis was marked. Head retraction had become evident; trismus was extreme. Lumbar puncture liberated a stream of fluid which was uniformly blood-stained. At midnight the patient was worse and exhibited increased stertor, cyanosis and hyperpyrexia. Slight movements of the face and upper limbs were apparent. Respiration became gradually more shallow, the pulse failed suddenly and death occurred at 3.25 a.m. on January 12.

The father and a sister of this boy developed smallpox after his removal to hospital; each passed through an uncomplicated modified attack of the disease.

Pathology.—Macroscopically the brain and cord showed considerable congestion. With the naked eye it was possible to detect around a few vessels in the white matter of the cerebral hemispheres greyish-pink translucent rings which later were found to coincide with the more extensive zones of perivascular demyelination. The lungs were congested and œdematous.

Microscopically, the lesions are typical of the acute perivascular myelinoclasis which follows certain exanthemata and are in all essentials similar to those occurring after vaccination. Perivascular infiltration with large and small lymphocytes, plasmacytoid cells and occasional plasma cells is more marked than usual, and cuffs several cells deep occupy the perivascular spaces in many parts of the brain and cord. This infiltration occurs in conjunction with the extra-adventitial changes mentioned below and also, particularly in the cerebral cortex, independently of such changes.

Extra-adventitial lesions consisting in wider or narrower zones of demye-

[1] For the reports on blood and cerebrospinal fluid we are indebted to Dr. V. D. Allison, L.C.C. Southern Group Laboratories, Hither Green.

lination with cellular accumulation occur around many of the vessels. (Fig. 1.) In these zones there is some outfall of axis-cylinders with degenerative changes in many of those persisting. The infiltrating cells are chiefly microglial, but where perivascular sheathing is intense lymphocytes and occasional plasma cells may be present in the nervous tissue immediately adjacent to the vessel wall. Fatty products of myelin disintegration are scanty, amounting usually to only a few fine Scharlach-staining granules in the microglial phagocytes. In a few areas of the meninges slight mononuclear infiltration is seen.

In some parts of the cortex there is a diffuse proliferation of microglia, mainly in the form of rod-cells; the cells are not nearly so closely packed as in the demyelinated areas of the white matter and their distribution bears a less obvious relation to the local vessels.

These changes are found in many areas of the cortex and white matter of the cerebral hemispheres; other areas are, however, wholly spared. The caudate nucleus is free from lesions and the lenticular nucleus shows only occasional slightly affected vessels. In the claustrum lesions are very marked. In the optic thalamus intense lesions are present immediately under the ependyma of the lateral ventricles. Throughout the brain-stem the areas of damage are for the most part confined to one side, the other half of the cross-section being almost normal. In the cervical cord this unilateral distribution is absolute, but at lower levels both sides of the cord participate in the inflammation. The grey matter is more severely damaged than the white, and while many vessels of the antero-lateral column are affected, only occasional zones of myelin destruction are found in the posterior columns. Changes of similar or less degree, but bilaterally disposed, are seen at all dorsal segments examined. The lumbar cord is more intensely affected; by coalescence of the zones around adjacent vessels the dense cellular infiltrate appears to be uniform over the whole of the grey matter, in which no myelin sheaths can be recognized. The zones of demyelination around the vessels of the white matter are very broad, and both posterior and antero-lateral columns are heavily involved.

Throughout the nervous system the nerve-cells exhibit mild toxic changes in no way related to the proximity of an affected vessel. Usually, even when situated in a densely infiltrated area, they are tolerably well-preserved, though in the cervical cord the anterior horn cells are definitely more damaged on the abnormal side. Contrary to the usual findings in this disease, in the lumbar region definite destruction of nerve-cells has taken place, especially in the anterior horns where necrotic masses with a phantom nucleus or without any apparent nuclear structure occupy the site of many of the large motor cells. Neuronophagia is not observed,

Of the other viscera only the lungs, in which a capillary bronchitis with areas of incipient bronchopneumonia are present, show any definite abnormality.

Case 2.—Q. G., aged 10, an unvaccinated girl, had suffered previously only from measles. On September 18, 1929, she fell ill with headache, backache

and vomiting: a smallpox rash appeared on the 21st. She was admitted to hospital on the 24th with a discrete vesiculo-pustular eruption of modified smallpox, type six. No other abnormality was then noted.

During the night she complained of severe pain "all up the back." Temperature 101° F., pulse 116, respiration 24. Urine was passed normally. On the morning of September 25 the patient had no power in her lower limbs, which lay flaccid in the bed. She still complained of pain in the back. Retention of urine was now present; enemata were not retained. At night the child was drowsy. Fourteen ounces of urine free from abnormal constituents were withdrawn by catheter.

On September 26 the girl would answer questions fairly intelligently, but it was difficult to hold her attention and she relapsed quickly into a drowsy state. Complete flaccid paralysis of both lower extremities was present, with total anæsthesia up to about the level of the twelfth dorsal vertebra; above this both movement and sensation appeared normal. Voluntary contraction of the abdominal muscles could not be elicited. The optic discs appeared normal. Plantar, tendon and abdominal reflexes were absent. Urine and fæces were retained.

On September 27, temperature 98·4° F. The patient was more wakeful. Anæsthesia now extended to the level of the seventh dorsal vertebra. Clear fluid escaped readily on lumbar puncture, of which the child felt nothing; this contained 74 cells per c.mm., all small lymphocytes. No organisms were seen and cultures on blood-agar were sterile.

The fluid also contained: sugar, 64 mgm. per 100 c.c.; chlorides, 684 mgm. per 100 c.c.; and protein, 0·07 per cent. The Nonne-Apelt test was negative.

On September 28 anæsthesia extended to about the level of the nipples, without any sharp line of demarcation.

On September 29 some return of sensation occurred over the trunk and legs, with hyperæsthesia on the abdomen; there was no change in the paralysis. The patient was again drowsy.

On September 30 drowsiness was less marked and the girl complained of pain in the thighs and over the lower abdomen. True urinary incontinence commenced. Lumbar puncture again gave a clear fluid; the insertion of the needle was now appreciated.

On October 1 the patient was incontinent of fæces for the first time. Normal appreciation of pin-prick on the trunk and hyperæsthesia over the legs were noted; thermal sense was very imperfect over the lower half of the body.

On October 2 lumbar puncture was repeated; the fluid contained 27 cells per c.mm., all small lymphocytes: sugar, 62 mgm. per 100 c.c.; chlorides, 725 mgm. per 100 c.c.; and protein, 0·07 per cent. The Nonne-Apelt test and the Wassermann reaction were negative.

By October 3 all signs of drowsiness had disappeared. Pain was again present in the right thigh. There was no hyperæsthesia, but the patient failed to discriminate between painful and other stimuli over the lower half of the body.

By October 5 some power had returned to the trunk muscles; the child could now roll herself over and struggle into a sitting posture.

On October 9, in spite of continued dribbling incontinence, the urine was still free from abnormal constituents; incontinence of fæces persisted. The patient experienced transient pain in the right foot. Cerebrospinal fluid escaped at an apparently normal rate. It contained 9 cells per c.mm., all small lymphocytes; sugar, 62 mgm. per 100 c.c.; chlorides, 713 mgm. per 100 c.c.; and protein, 0·14 per cent. The Nonne-Apelt test was negative.

On October 16 a plantar response, indeterminate in direction, was elicited on the right side.

On October 17 the skin broke over a small area at the summit of the natal cleft.

By October 19 early spasticity, more marked in the right than in the left leg, was apparent, with a definite extensor plantar response on the right side. Pin-pricks were not appreciated as painful on the legs. Sphincter disturbances had not improved.

October 26 the patient was able voluntarily to contract the abdominal muscles, to flex and extend the great toes, and to a limited degree to flex the legs at the hip-joints. While she could discriminate between and accurately localize pin-prick and light touch, differences of temperature were still very imperfectly appreciated, particularly over the lower part of the back and the upper part of the thighs. Plantar stimulation of either sole elicited an extensor response of the corresponding great toe and foot and a flexor response of the limb as a whole.

By October 30 urine was being voided unconsciously in a reflex manner about every two hours; it remained free from any abnormality. The lower limbs were more spastic. Sensation appeared normal.

By November 6 the child, if supported, could stand and make a few steps. Knee and ankle jerks were more marked on the right side. Only the left upper abdominal reflex could be obtained. Adductor and ham-string spasm began to be apparent, and by November 13 there was a strong tendency to flexion, adduction and internal rotation of the legs. On November 16 return of rectal sense was first apparent. On November 27 the patient could stand unsupported. Muscular spasm had diminished. Extensor and crossed flexor plantar responses were obtained. The patient had limited but definite control of bowel and bladder. Progress hereafter was steady; spasticity diminished and power returned in the lower limbs. Bowel and bladder consciousness and control gradually returned to normal.

The patient was discharged from hospital on January 9, 1930. Her mental state was considered normal. In the lower limbs some spasticity was apparent; muscular power was good; knee and ankle jerks were exaggerated; ankle clonus absent; the plantar responses were extensor, with flexor leg response more marked on the right side. Only the left upper abdominal reflex could be obtained.

In March, 1931, the patient was seen by Dr. Bernard Schlesinger, who has

kindly supplied the following notes of her condition. Mentality normal. Knee and ankle jerks markedly increased; abdominal reflexes present: plantar responses extensor. Some spasm of the adductors of the legs again noticeable; plantar flexion of feet developing.

Two brothers and a sister of this patient subsequently developed smallpox; they remained free from nervous symptoms.

Case 3.—A. Y., a boy, aged 8, had suffered previously from chickenpox, measles and pneumonia. A brother was removed to hospital with smallpox on December 26, 1929, and on 28th A. Y. was primarily vaccinated in one insertion; vaccination was successful.

On January 8, 1930, A. Y. was admitted to hospital with a discrete pustular modified smallpox rash (type six), estimated to be at about the sixth day of development. On the outer surface of the left upper arm was one vaccinia pustule surrounded by a normal zone of reaction. The conjunctiva of the right eye was inflamed. The patient was afebrile.

On the morning of January 12 he was allowed up, but a few hours later he was noticed swaying as he walked. He complained only of feeling tired. The temperature, previously subnormal, had risen to 101° F., pulse 98, respiration 22. About noon the boy was drowsy but could be roused to answer questions, although his articulation was slurred. Breathing was stertorous. A right internal strabismus and weakness of the facial muscles on that side were apparent. The abdominal reflexes were absent. No rigidity or paralysis was obvious in the limbs. The right knee-jerk was absent; both ankle-jerks were present. The plantar response was flexor on the right side, extensor on the left. Kernig's sign was absent. No impairment of sensation to pin-prick was apparent. The vaccinia lesion was crusting, with little surrounding tissue reaction and no undue adenitis. On lumbar puncture clear fluid escaped rapidly.

On January 13 the patient was semiconscious; he lay quietly and breathed normally. Squint had disappeared; but facial weakness was still present. Kernig's sign was positive. The abdominal reflexes and ankle-jerks were absent; knee-jerks were present; plantar responses were indefinite. Dribbling of urine was not associated with distension of the bladder. The boy appeared unable to swallow. Clear fluid, the last portion mixed with blood, escaped rapidly on lumbar puncture. It contained 483 red and 542 white cells per c.mm.; a differential count of white cells showed 43 per cent. polymorphs., 53 per cent. small lymphocytes, and 4 per cent. large mononuclears. No organisms were seen and cultures were sterile. The fluid also contained sugar, 60 mgm.; chlorides, 749 mgm. per 100 c.c., and protein, 0·08 per cent. The Nonne-Apelt test was negative.

On January 14, the temperature ranged from 97° F. to 100·2° F. The boy was unconscious. The limbs were flaccid and knee-jerks could not be obtained; Kernig's sign was absent; otherwise the physical signs were unchanged. Catheterization yielded about 12 oz. of acid urine containing a trace of acetone. About 25 c.c. of clear fluid, the last portion tinged with blood, were

obtained by lumbar puncture. Examination showed white cells 345 per c.mm. and numerous red cells, protein 0·09 per cent. The Nonne-Apelt test and the Wassermann reaction were negative. The blood gave a negative Wassermann reaction and contained 41 mgm. per cent. urea.

On January 15 the patient lay unconscious and completely immobile with saliva running from the side of the mouth; 30 c.c. of clear fluid were removed by lumbar puncture and 15 c.c. of human convalescent smallpox serum injected. At night the temperature rose to 102·4° F. On January 16 cyanosis was apparent, salivation was more marked, and spasmodic twitching occurred on the left side of the face. The plantar reflexes were extensor. Retention of urine and fæces persisted and acetonuria was present. Cerebrospinal fluid, slightly hazy from admixture with blood, was withdrawn by lumbar puncture.

On January 17 the temperature became subnormal and the pulse fell to 60. A small crop of herpetiform vesicles was noticed on the paretic side of the mouth. By putting up his hands to the areas stimulated the patient responded to a touch anywhere on the face. A differential count of white cells present in the cerebrospinal fluid showed: 22 per cent. polymorphs., 74 per cent. small lymphocytes, and 4 per cent. large mononuclears. The fluid contained 0·10 per cent. protein, and the Nonne-Apelt test was negative.

On January 18 purposeful movement of limbs was noted and milk was swallowed from a spoon; pin-prick seemed to be appreciated generally. Lumbar puncture was repeated. At night the patient was incontinent of urine. On January 19 the boy was again deeply unconscious. Intermittent incontinence of urine (containing a cloud of albumin) became established. At night the patient sometimes answered when addressed. Marked sweating of the head was apparent. Cerebrospinal fluid was clear and escaped readily on lumbar puncture.

On January 21 the cerebrospinal fluid appeared to be under greater pressure. The patient was brighter and answered questions readily. The plantar responses were flexor; the left knee-jerk only was obtained. Frequent nose-rubbing was now evident for some days. On January 22 both ankle-jerks and the left knee-jerk were elicited. Fæces were retained; incontinence of urine continued. Lumbar puncture was repeated.

On January 25 facial weakness was less obvious and the patient had regained some control over micturition; the urine still contained some albumin. Abdominal reflexes and knee-jerks could not be obtained; ankle-jerks were present.

On January 27 the patient was mentally alert. No difficulty in deglutition, mastication or articulation was evident and nasal feeding was discontinued.

By February 2 the boy could sit up in bed and read. The urine was free from abnormal constituents. Micturition and defæcation were normal. The abdominal reflexes were still unobtainable, but ankle-jerks, knee-jerks and flexor plantar responses were present. After return to consciousness masturbation was a troublesome feature.

On February 4 the patient sat up in a chair and a few days later commenced walking exercises. Rapid progress was made and general bodily wasting soon disappeared.

On February 27 the patient was discharged from hospital. The general condition was good and the mental state appeared normal. The boy presented some monotony of expression, but according to his parents this had always been so. Speech was slow but not scanning and articulation was normal. There was no paralysis. Knee and ankle jerks were present; the plantar responses were flexor; the abdominal reflexes were still wanting. Four months later the boy's mother wrote to say that he was leading a normal life at school.

H. Y., an unvaccinated brother of this patient, was removed to hospital on December 26 and passed through an uncomplicated attack of smallpox. Two other brothers, J. Y. and R. Y., were successfully vaccinated on December 28 and 30 respectively; both developed smallpox which ran an uncomplicated course. It is worthy of note that J. Y. was vaccinated on the same day as A. Y., possibly with the same batch of lymph.

The onset of nervous symptoms in the case of A. Y. occurred on the sixteenth day of successful primary vaccination and about the ninth day of a smallpox rash. The incubation period is within the limits attained by cases of acute perivascular myelinoclasis following either vaccinia or variola, but more closely approximates to the mean average of those associated with the latter disease.

Case 4.—H. R., an unvaccinated man aged 21, had in childhood suffered from measles and pneumonia. His present illness commenced insidiously. A smallpox rash appeared on January 6, 1930, and on 10th the man was admitted to hospital with a discrete pustular eruption of modified smallpox (type six). On 12th he was allowed up.

On the morning of February 18 he felt giddy and sleepy and had to be assisted back to bed. The temperature was not raised. In replying to questions the speech was slow. During the night he was incontinent of urine.

On February 19, temperature 99·2° F., pulse 92, respiration 20. The man complained of headache and pain in the legs, and was dull and confused. Some cervical rigidity was present. The pupils were small, equal, and reacted to light. Kernig's sign was absent; knee and ankle jerks and abdominal reflexes were not obtained; plantar responses were flexor. At night the man was semi-conscious but could be persuaded to answer questions. Pain in head and legs had ceased. Retention of urine was relieved by the catheter; the urine was normal. Fæces were retained. Weakness of the right face was noted; otherwise the cranial nerves were normal, as were the upper extremities. In the lower limbs, however, very little power existed. The patient could just move his toes and feet. Voluntary muscular contraction in the legs was perceptible, but limited and ineffectual. Both legs were flaccid; the knee and ankle jerks were wanting; the plantar responses were flexor. Abdominal reflexes were absent. No sensory loss was detected.

On the morning of February 20, temperature 100·6° F., pulse 86, res-

piration 20. Large bullæ had appeared on the dorsum of the left foot, on the extensor surface of the left great toe, and over the left hip. The patient was conscious, but drowsy and dull. Clear fluid escaped readily on lumbar puncture. This contained 470 cells per c.mm., of which 358 were red and 112 white, 1 per cent. polymorphs, 96 per cent. small lymphocytes, and 3 per cent. large mononuclears. Cultures were sterile, and no organisms were seen. The fluid also contained sugar, 80 mgm. per cent.; chlorides, 743 mgm. per cent.; and protein, 0·10 per cent. The Nonne-Apelt test and the Wassermann reaction were negative; blood contained 64 mgm. urea per cent.

At night the patient was more stuporose and mostly lay immobile, but at times ground his teeth. The pupils were small and barely reacted to light; an intermittent right external strabismus was evident. The plantar responses were not obtainable. Pin-prick on the face, arms and hands elicited movements of resentment; elsewhere it was apparently not appreciated.

On February 21, at times the man appeared to be fully conscious. Squint was no longer evident. Weakness was now noted in the arms, more especially in the right; pin-prick was appreciated above the level of the nipples. A flexor plantar reflex was obtained on the left side. Clear fluid under great pressure was withdrawn by lumbar puncture, and 10 c.c. human convalescent smallpox serum injected intrathecally. At night teeth-grinding and twitching of the left face occurred.

On February 22 the man was mentally clearer and more able to keep awake. He could move his head from side to side, but was unable to raise it from the pillow. Weakness was more marked in the right than in the left arm; no voluntary contraction of the muscles of the abdominal wall could be made out. The lower limbs were flaccid and powerless; the condition of their reflexes was unchanged. Pin-prick was appreciated as a blunt sensation over feet and ankles; above this anæsthesia was complete to the nipple level, after which pin-prick seemed sharp and painful. Shooting pains were felt in the arms. About this time priapism commenced to be a troublesome feature.

On February 23 the patient complained of pain in the neck, which was stiff but not retracted. Lumbar puncture was repeated, and for the first time the man experienced pain during it.

On February 24 the patient slept a great deal but was quite intelligent when roused. He perspired freely. Painful plantar stimulation elicited a flexor leg response, more marked on the left side, without any definite movement of the great toe. Sharp and blunt points were correctly appreciated on the head, neck, chest and upper limbs. The skin over the abdomen was insensitive. Sharp was interpreted as blunt on both lower limbs.

By February 26 drowsiness had disappeared. The man was incontinent of urine and he complained of pains in the legs; in the left foot he had limited power of voluntary movement. Plantar stimulation elicited an extensor great toe and a flexor leg response, more obvious on the left side. Facial palsy was no longer apparent. Arms were equal in strength. No area of the body was now insensitive to light touch, but thermal sense was imperfect on the lower extremities and absent on the trunk below the nipple level.

Examination of cerebrospinal fluid revealed 102 red cells and 29 white cells, all small lymphocytes, per c.mm.

The fluid contained sugar, 66 mgm. per cent.; chlorides, 731 mgm. per cent.; and protein, 0·035 per cent. The Nonne-Apelt test was negative.

On February 27 dribbling incontinence of urine (containing albumin) and fæces became established. The patient could now move both feet. The following night the temperature was above normal for the last time.

On March 1 signs of mental change became apparent. The man began to make curious statements, asserting, for example, that he had not slept for a week. He was still unable to raise his head or trunk. In the lower limbs movement was limited to the feet, but obvious though ineffectual contractions of the thigh muscles occurred on voluntary effort.

On March 3 the patient at first sight seemed bright and intelligent. In the course of conversation, however, he showed signs of a disordered imagination in remarkable and chiefly grandiose statements which were obviously untrue. His memory for recent events was good.

He now passed urine reflexly and unconsciously at intervals; fæces also were voided without his knowledge. The grip was stronger and equal on the two sides. Power was returning to trunk and legs. Each leg was withdrawn from plantar stimulation and the left great toe gave an extensor response. The right knee-jerk could just be elicited. Pin-prick was everywhere appreciated.

On March 6 the patient talked more rationally but was excitable and emotional. Power had increased in the lower limbs. He possessed some knowledge of impending micturition but lacked inhibitory power. On March 8 rectal sense begun to return.

By March 12 the man seemed mentally normal. He could stand with support and make a few steps. The upper limbs were normal. Knee and ankle jerks were absent, plantar responses extensor. Sensation was normal apart from some loss of thermal sense on the feet and legs. A few days later pus and *B. coli* appeared in the urine; this infection lasted for about three weeks.

By March 18 knee-jerks, ankle-jerks and ankle-clonus were present. Plantar responses were extensor, abdominal reflexes absent. Sphincter control was returning gradually. The patient denied any knowledge of his earlier irrational statements.

On April 24 the man was discharged from hospital in a nearly normal condition. There was some spastic weakness of the lower limbs with exaggerated tendon reflexes, extensor plantar responses and absent abdominal reflexes, and sphincter control was not entirely reliable.

The father, mother, sister and two brothers of the patient followed him to hospital with uncomplicated attacks of smallpox.

Case 5.—G.B., an unvaccinated boy aged 15, had suffered previously from chickenpox, measles and diphtheria. On February 9, 1930, he fell ill with headache and malaise, and on 14th was admitted to hospital with a modified

smallpox eruption (type six) estimated to be at the fourth day of development. The temperature was 99° F. but fell to 98.4° F. on the following day. During the afternoon of February 16 the boy complained of frontal headache, and at night the temperature was 99° F.

On February 17 the patient had slept soundly but awoke with more pronounced headache. He was drowsy, responded unwillingly to questions, and resented interference. Head retraction, Kernig's sign, and tache cérébrale were present. The cranial nerves were normal. The abdominal reflexes were absent; Babinski's sign was present on each side; the left knee-jerk was sluggish and the right was not obtained. Lumbar puncture was performed. In the cerebrospinal fluid no tubercle or other organisms were seen, and cultures were sterile. The fluid contained 490 cells per c.mm., 87 per cent. polymorphs., 8 per cent. small lymphocytes and 5 per cent. large mononuclears; sugar 85 mgm. per 100 c.c., chlorides 743 mgm. per 100 c.c. and protein 0·076 per cent. The Nonne-Apelt test was negative. The Wassermann reaction was negative in cerebrospinal fluid and blood. The blood contained 42 mgm. urea per cent.

At night, temperature 103° F., pulse 144, respiration 40. Occasionally the patient moved the head and arms but mostly lay still with laboured breathing, saliva running from the mouth, and profuse perspiration on the head. It was impossible to rouse him. The pupils were equal in size and reacted to light; an intermittent bilateral convergent strabismus was present. Head retraction had diminished. The upper limbs had a certain rigidity; the legs were flaccid and motionless. Abdominal reflexes and tendon-jerks were absent. Strong stimulation elicited extensor plantar responses. Anæsthesia to pin-prick was complete up to the nipple level. Urine, obtained by catheter on account of retention, was free from abnormal constituents. Clear cerebrospinal fluid under increased pressure was withdrawn by lumbar puncture and 15 c.c. human convalescent smallpox serum injected. After a few hours the temperature rose to 105° F. but soon dropped to 103° F.

On February 18 the boy was deeply unconscious; he made no attempt to swallow saliva which dribbled from the mouth. An extreme degree of trismus made it impossible to force open the mouth. The arms, which were moved from time to time, were semi-rigid and flexed at the elbows; spasm, particularly noticeable on attempt to raise the left arm at the shoulder, relaxed before repeated passive movement. The head and lower extremities remained motionless. A large bulla had arisen spontaneously over the left external malleolus. Lumbar puncture was performed in the evening and clear fluid under considerable pressure withdrawn.

On February 19 the boy was comatose and immobile; breathing was quiet but marked by an occasional deep sigh. Trismus was less marked and strabismus no longer apparent. All the limbs were flaccid and devoid of tendon reflexes. In spite of careful nursing, fresh bullæ had appeared over the heels and back. Lumbar puncture was repeated. Next day, save for incontinence of urine, the clinical condition was unchanged. Lumbar puncture was repeated.

On February 21 the patient was incontinent of fæces; he moaned occasionally. Lumbar puncture yielded clear fluid with yellowish tinge; 8 c.c. human convalescent serum were injected. On February 22 the patient again perspired freely about the head and excessive salivation was apparent, though swallowing was possible with difficulty.

On 23rd the boy repeatedly opened the eyes but remained unresponsive to stimulation. On 24th movement in response to pin-prick included rolling of the eyes and slight jerking of the head. Trismus was less marked and swallowing easier. The arms, especially the right, were again rigid. On 26th the boy moved the arms slightly and when addressed in a loud voice groaned as though attempting to reply. On 27th an intermittent bilateral convergent or divergent strabismus was again evident and was present at intervals for several days. Lumbar puncture was repeated. The fluid withdrawn on February 24 contained 42 cells per c.mm., 91 per cent. small lymphocytes and 9 per cent. large mononuclears; sugar, 95 mgm. per 100 c.c.; chlorides, 778 mgm. per 100 c.c.; and protein, 0·085 per cent. The Nonne-Apelt test was negative.

On March 1 the patient could move head and arms and make groaning attempts to speak. On the right side an extensor plantar response was present; on the left side plantar stimulation elicited weak contraction of the thigh muscles without movement of the foot or great toe. Lumbar puncture was repeated next day.

On March 3 dribbling incontinence ceased and urine was passed unconsciously in small quantities once or twice an hour; it contained some albumin but was free from pus. Retention of fæces alternated with incontinence. The boy was regaining consciousness slowly. Trismus persisted but the patient was able to swallow small quantities of liquid from a spoon. Cerebrospinal fluid withdrawn on March 4 contained 12 cells per c.mm., all small lymphocytes; sugar, 90 mgm. per 100 c.c.; chlorides, 760 mgm. per 100 c.c.; and protein, 0·06 per cent. The Nonne-Apelt test was negative.

On March 6 the patient appeared to understand what was said to him but was still unable to speak; in spite of great efforts to do so the only result was a moaning noise. Voluntary movement of the upper limbs was very limited and the grip excedingly weak. Some voluntary movement was possible in the right foot. Babinski's sign was present and more marked on the right side. Pin-prick was appreciated except over the left lower extremity. Next day the boy was still unable to articulate but made loud noises in his efforts to form words; his state was highly emotional.

On March 9 articulation had improved to the extent that words were mostly intelligible, though possessed of a groaning quality; there was no special difficulty in pronouncing any letter of the alphabet. The boy was bright and alert but was very emotional. His memory for recent and remote events was surprisingly good and he gave an estimate, approximately correct, of the duration of unconsciousness. He could turn his head but was unable to lift it from the pillow. All movements of the right arm could be carried out

voluntarily but weakly; in the left arm slight movement at the wrist alone was possible. He complained of pain in these limbs. He was able to move the right foot and contract the thigh muscles, but on the left side voluntary power was wholly lacking. Anæsthesia to light touch prevailed over the buttocks and sacrum and over the left lower extremity where pin-prick also was appreciated as a blunt sensation. Thermal sense was deficient over both lower limbs. Wasting was marked.

By March 11 the boy talked incessantly. He began to suffer from delusions. He imagined that one of his nurses had fallen and cut her head, and maintained that he had something in his left arm put there by the nurse each night, and which he demanded should be removed. So persistent was this latter obsession that one was led to consider whether he had any recollection of a few hypodermic injections of atropine given at a time when he was salivating excessively and when he was thought to be in a profoundly unconscious state. Two days later cystitis occurred as a complication.

By March 18 articulation was normal. The patient was quieter and less emotional but had assumed the attributes of a spoiled and naughty child. He was unwilling to move the left arm, particularly at the shoulder-joint, persisting that it pained him when touched. Free voluntary movements at finger, wrist and elbow-joints and limited movements at the shoulder were possible. Power had improved considerably in the right arm, though fine finger movements were not possible; an intention tremor was present. Lateral nystagmus was noted. The patient could write in a clumsy fashion. Masturbation became a troublesome feature.

By March 26 the mental state was almost normal and the boy expressed regret for his earlier misdeeds. He now spoke with a stammer, an old impediment for which he had attended a speech clinic; this had been present on admission to hospital, absent during the loquacious and emotional stages of the illness, and had returned with improvement in the mental state. Bladder and rectal control had increased. The right arm was stronger and intention tremor no longer present. The grasp of the left hand remained weak, but movements of the forearm and at the shoulder-joint were free and pain was absent. Power in the trunk muscles had increased and the patient could make an effort to stand; the left leg was still weaker than the right. Both knee-jerks were present. Cutaneous sensibility was almost normal.

On April 2 the boy could place his left hand on the top of the head; an intention tremor was now present in this limb. On April 8 the right upper abdominal reflex was obtained, and on April 10 both right reflexes.

While strength increased and he was able to walk, the mental and moral state regressed, and again he became wilfully naughty, recommenced masturbation, and seemed determined to make no effort to regain control over his sphincters. His old trophic lesions again broke down and a new one appeared over the right great trochanter, necessitating a return to bed.

The patient was eventually discharged from hospital on June 6. At that time incontinence had not occurred for two weeks and the behaviour had for

some time been consistently good. Wasting of the left arm was apparent, a coarse intention tremor was present, and fine movements could not be performed with the fingers of that limb. Otherwise power and movement in the upper extremities were good, and all tendon reflexes were obtainable. At times a lateral nystagmus was present. The left lower abdominal reflex was absent. Power was good in the lower limbs and the boy walked well. Tendon-jerks were present, on the left exaggerated and with ankle clonus. The left plantar response was extensor, the right indefinite. Sensation was normal. Trophic lesions had healed. The urine was free from abnormal constituents.

The patient was seen again on May 31, 1931, nearly a year later, when he cycled from his home about twelve miles away. Since his discharge he had worked continuously as a barber's assistant. Mentality appeared normal, though the rather excitable, nervous manner was still evident and the stammer persisted. Power was normal in the limbs and fine movements of the fingers were well performed. The right tendon-jerks were present, the left slightly exaggerated with ankle clonus. The left plantar response was extensor, the right indefinite. Nystagmus and intention tremor were absent.

Case 6.—K. C., an unvaccinated girl aged 7, had suffered previously from measles, chickenpox and diphtheria. On April 12, 1931, she fell ill with headache and pain in the limbs, and a smallpox rash appeared on 14th.

On April 19 the patient was admitted to hospital with a pustular modified smallpox rash (type six). Temperature 102° F., pulse 96, respiration 22. She was feverish and complained of headache; a follicular deposit was present on each tonsil. No abnormality was found on examination of the heart, but in the lungs a diffuse bronchitis and signs of early pneumonia at the right base were detected. A culture from the throat showed no diphtheria bacilli.

At 11.30 p.m. the patient was unconscious; she groaned but could not be induced to speak. There was retention of urine. The limbs were moved in response to stimulation and there was, apparently, no anæsthesia. Dysphagia and trismus were present; the palate moved normally. The pupils were equal in size and reacted sluggishly to light; an intermittent divergent strabismus was noted. Corneal reflexes were present, abdominal reflexes absent. The knee, but not the ankle-jerks were obtained; plantar responses were flexor. Head retraction and Kernig's sign were absent. Lumbar puncture readily yielded clear, colourless fluid.

On April 20 the girl was deeply unconscious, slightly cyanotic, and quite unable to swallow. Trismus was well-marked but squint was no longer evident. The head was a little retracted. The limbs were moved sluggishly in response to stimulation. Tendon reflexes were present in the arms only. True incontinence of urine was present.

At 1 p.m. 15 c.c. of cerebrospinal fluid were withdrawn by lumbar puncture, and 10 c.c. of convalescent smallpox serum injected. In the fluid no tubercle bacilli were found but cultures gave a pure growth of *Staphylococcus aureus*, which appeared to be a contamination. There were 339 red blood-cells, and 36 leucocytes per c.mm., 30 per cent. polymorphs., 64 per cent. small

lymphocytes, and 6 per cent. large mononuclears; sugar, 95 mgm. per 100 c.c.; chlorides, 702 mgm. per 100 c.c.; and protein 0·02 per cent. The Wassermann reaction was negative.

At night, temperature 104·4° F., pulse 110, respiration 38. Dyspnœa increased, cyanosis was more marked and the pulse showed signs of failing. The lungs were full of coarse bubbling râles. Death occurred at 6.30 a.m. on April 21.

Three sisters and two brothers of this patient contracted smallpox from her but experienced only minor complications. The mother of the family, who had been vaccinated in infancy, was successfully re-vaccinated and admitted to hospital with the youngest child whom she was nursing; she remained in good health.

Pathological examination.—Macroscopically the brain showed only congestion. Cultures yielded a short-chained streptococcus; later, in histological preparations, the vessels in many of the organs were seen to be filled with similar organisms indicative of a terminal bacteriæmia. The lungs were the seat of diffuse bronchitis with early bronchopneumonia at the right base.

Microscopically, typical lesions exist around the vessels, especially the veins, and are roughly symmetrical in the two hemispheres. Meningeal infiltration is limited to small areas where mononuclear cells are collected in the meshes of the pia-arachnoid. Perivascular infiltraton with large and small lymphocytes and a few large mononuclears is of moderate intensity; around many vessels only a single layer of cells is present, around others the ring is three or four cells deep. In the extra-adventitial tissues the usual broad zone of microglial cells, some with highly polymorphic nuclei and a few showing karyorrhexis, includes also scanty lymphocytes, and is accompanied by demyelination and the appearance in the phagocytic cells of tiny granules of Scharlach-staining material.

Such changes are of medium severity throughout the white matter of the hemispheres and in the cerebral cortex, where an extra-adventitial infiltrate is more diffuse and less sharply delimited peripherally. Mild lesions are present in the caudate nucleus, globus pallidus and anterior part of the putamen, severe lesions in the posterior part of the putamen, claustrum and capsulæ externa and extrema. Lesions are less marked in the brain-stem than is often the case, and the white matter of the cerebellum is only slightly affected.

Most segments of the spinal cord are normal; of twelve levels examined only four from the upper dorsal and lumbar regions show typical changes. In a few of the remaining sections some swelling of the myelin sheaths, unaccompanied by cellular infiltration, is apparent at the periphery of the cord or along the lips of the anterior fissure.

In all parts of the central nervous system the nerve-cells are well-preserved or, where situated in a densely infiltrated zone, exhibit only mild degenerative changes.

Of the other organs, the liver shows well-marked mononuclear infiltration around the vessels of the portal tracts, and mild fatty changes of diffuse

distribution in the liver cells. The spleen is greatly congested. The left lung is congested and œdematous, with bronchitis in some of the smaller tubes but no bronchopneumonia; the right is the seat of a definite bronchopneumonia.

Case 7.—The following case occurred at Stoke-on-Trent. For the ensuing clinical account and for permission to include it in this series we are indebted to Dr. A. J. Ewing.

On April 14, 1930, W. B., an unvaccinated boy aged 13, fell ill with headache, backache, and vomiting. On 18th a smallpox rash was noticed, and on 19th the boy was admitted to hospital; the eruption was mild and there were no general symptoms.

On the morning of April 22 the lad appeared quite normal. At 12.30 p.m. he was thought to be asleep and no attempt was made to waken him; later in the afternoon it was found that he could not be roused. He lay relaxed with legs slightly flexed and without head retraction. The arms were flexed and stiff; the wrists were strongly flexed with thumbs held in the palms between the second and third fingers. There was some resistance to passive movement at shoulder- and elbow-joints, and to a less degree at the wrist. The pupils were equal and reacted to light, but varied in size from time to time; there was no nystagmus, squint or ptosis. Knee-jerks were absent and there was no ankle clonus; plantar responses were flexor.

Between April 22 and 24 the clinical condition remained almost unchanged. Fæces were retained; urine was passed involuntarily. Swallowing was difficult. The only response which could be obtained from the boy was a faint groan when attempts were made to extend the arms. The head remained freely movable. On 23rd 8 c.c. clear fluid under normal pressure was withdrawn by lumbar puncture; after centrifuging only an occasional polymorph was seen. On 24th the patient showed signs of collapse. Temperature 102° F., pulse 126.

On the morning of April 25 the patient lay on his back as before; he was unconscious and breathing stertorously. The neck and the legs were free from rigidity; the arms had at first a certain stiffness, disappearing after repeated passive movement. All reflexes were absent from the right arm and leg; on the left side knee-jerk, plantar response and triceps-jerk could just be obtained. The pupils reacted briskly to light; they were regular and equal but varied in size at different examinations. The boy was emaciated and swallowed only with difficulty. Death occurred during the day.

Pathological examination.—The chief macroscopical findings were intense congestion of the brain, particularly marked in the white matter, and congestion of both lungs with capillary bronchitis and areas of bronchopneumonia at the base. Cultures of brain and blood proved sterile.

Histologically the lesions are typical and are identical with those occurring after vaccination. In many parts of the nervous system both arteries and veins have mild perivascuular cuffing with lymphocytes and a few large mononuclear cells; sometimes a few lymphocytes may be found also in the nervous substance outside the vessel wall. Small patches of meningeal infiltration with similar cells occur in places. Many of the veins are surrounded

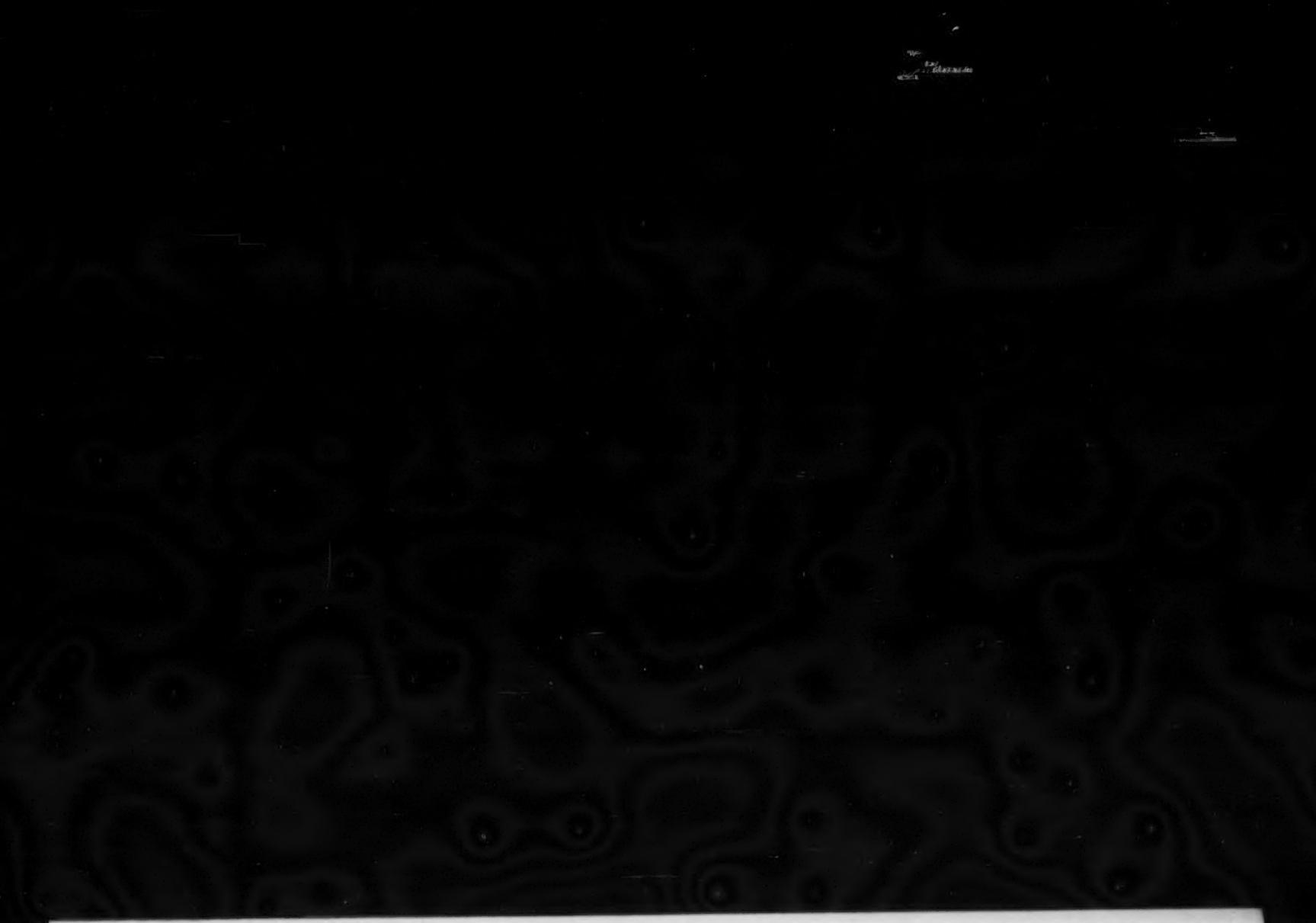

FIG. 1. *Case* 1.—Perivascular demyelination in white matter of cerebral hemisphere. Weigert-Pal.

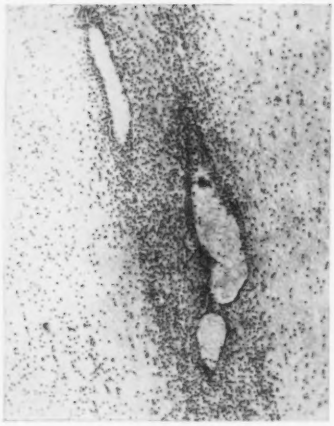

FIG. 2. *Case* 7.—Low-power view of affected vessels in white matter of cerebral hemisphere. Iron-alum-hæmatoxylin and eosin.

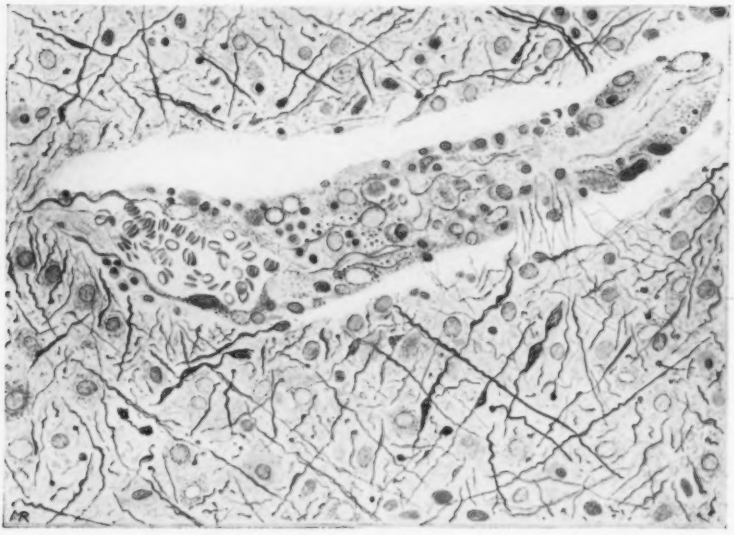

FIG. 3. *Case* 7.—Drawing from a Bielschowsky preparation of a zone of perivascular demyelination. Although many of the axis cylinders show degenerative changes, these structures are not completely destroyed as are the myelin sheaths.

To illustrate paper by J. Pickford Marsden and E. Weston Hurst.

by a broad extra-adventitial zone of cellular infiltration associated with complete demyelination of the nerve-fibres; in stained sections these lesions are readily visible to the naked eye. (Fig. 2.) Not infrequently coalescence of the zones around adjacent vessels has taken place. The cellular reaction here is almost wholly microglial, though a few glial cells with swollen nuclei are also present. In spite of the extensive destruction of myelin sheaths, fatty granules are far from abundant. The axis-cylinders passing through the demyelinated zones often show swellings and varicosities, but are not completely destroyed as are the myelin sheaths. (Fig. 3.) Where the grey matter is involved, some chromatolysis without nuclear changes may be present in the nerve-cells; more severe degeneration is not observed and no outfall of nerve-cells is apparent.

These lesions are well marked in the white matter of the cerebral hemispheres and in parts of the cortex, although in the latter simple perivascular cuffing is more commonly encountered. The island of Reil is most heavily involved. The basal ganglia are particularly severely affected; the caudate nucleus, lenticular nucleus and optic thalamus all contain extensive lesions. In the mid-brain and pons lesions are scanty, and the medulla, cervical and upper dorsal cord are wholly free from abnormality. Changes reappear in the lower dorsal cord and below that increase to a maximum in the lumbar region where they are very intense and affect both grey and white matter. The zone of demyelination so frequently seen beneath the ependyma of the lateral ventricles is of very limited extent in this case, and, except in the lumbar region, no strip of demyelination is seen at the periphery of the cord or along the lips of the anterior fissure.

The lungs contain areas of capillary bronchitis and early bronchopneumonia. The liver shows some congestion, especially in the central parts of the lobules. The other organs present no definite microscopical abnormality.

Group II.

Between September, 1929, and February, 1930, five cases of acute perivascular myelinoclasis occurred amongst 2,400 patients admitted to the London smallpox hospitals. During the same period eight other patients exhibited a syndrome characterized by drowsiness and pyrexia. Though commonly this state was transient and abnormal physical signs scanty, the symptoms suggested mild or abortive attacks of the above malady, and the cases were tentatively classed as "borderline cases." This suggestion gained strength from the absence of any other demonstrable complication or intercurrent disease to account for the symptoms, from the temporal relation to the attack of smallpox, which was that of acute perivascular myelinoclasis, and from the fact that the cases were encountered only about the time when the latter disease was occurring in the hospital. Careful observation of over 8,000 cases of smallpox

before and since this period has failed to reveal further examples. In all the "borderline cases" symptoms were so mild and transient that lumbar puncture was considered unjustifiable.

The following case is recorded as being fairly typical of the whole group; here symptoms commenced on the seventh day of the rash.

Case 8.—E. H., a girl aged 14, was primarily but unsuccessfully vaccinated on January 6, 1930, when her father and sister were removed to hospital with smallpox. On 9th she complained of headache and malaise; on 11th a smallpox rash made its appearance. The patient was admitted to hospital on 15th with a discrete pustular modified eruption (type six). The temperature was 98·4° F. and there were no general symptoms.

On the morning of January 17 the ward sister reported that the child had felt faint. She was in a drowsy state and resented being roused: with difficulty she could be persuaded to reply to questions. Absence of the right knee-jerk and of both ankle-jerks were the only abnormal physical signs. When seen again about half an hour later the child spoke intelligently and had almost completely lost her stupor.

Later in the day, temperature 98·4° F., pulse 104, respiration 24. The girl again became very drowsy but it was possible to rouse her to answer questions. The bowels had not been opened during the day; the patient had passed 5 oz. of urine (free from abnormal constituents) and the bladder was not palpable.

On January 18 the girl was free from symptoms. On examination, absence of knee-jerks was the sole abnormality noted. At night the temperature rose to 101° F., but resumed the normal level on the following morning.

The knee-jerks remained absent for a time; apart from this convalescence was uneventful.

The following case, which appears definitely to belong to the first group, is included here rather than there as occupying a position intermediate between the cases of acute perivascular myelinoclasis detailed already and the "borderline cases" typified by the one just recorded. Though more pronounced than in the last case, symptoms, commencing on the tenth day of the rash, were mild, and in a week from the onset the patient had apparently recovered completely. With this link connecting the two groups, and in view of the facts stated as introduction to the preceding case, it seems impossible to escape the conclusion that the "borderline cases" represent abortive attacks of the morbid condition responsible for the graver illnesses of the first group of cases.

Case 9.—J. F. H., an unvaccinated boy aged 14, gave no history of previous illness. On October 10, 1929, he suffered from headache and malaise; a smallpox rash appeared on 13th. On 20th he was admitted to hospital. His

eruption (modified, type six) was commencing to crust; pyrexia and general symptoms were absent.

On October 22, temperature 100° F. The patient vomited on several occasions and was drowsy. Apart from conjunctivitis in the left eye nothing abnormal was discovered on physical examination.

On October 23 the patient was incontinent of urine and fæces, very drowsy and strongly resentful of interference. He lay curled up on his left side with knees drawn up. He complained of severe frontal headache. The pupils were equal and reacted to light. Abdominal reflexes were absent, knee-jerks brisk, and plantar responses extensor. Kernig's sign was positive but the head was not retracted. Clear cerebrospinal fluid readily escaped on lumbar puncture. At night short periods of restlessness were interposed but the boy's state was mainly one of stupor.

On October 24 the boy was more rational and submitted more readily to examination, but he was still somnolent and maintained his characteristic curled-up attitude. Incontinence had ceased and the urine now contained a trace of albumin. The cranial nerves and optic discs were normal. Abdominal reflexes were elicited with difficulty; knee-jerks were normal, plantar reflexes extensor. Kernig's sign was present. On the outer aspect of the right thigh appreciation of light touch and thermal sense were deficient. Lumbar puncture yielded clear fluid under apparently normal pressure. Cultures were sterile. The fluid contained 58 cells per c.mm., all small lymphocytes; sugar, 58 mgm. per 100 c.c.; chlorides, 708 mgm. per 100 c.c.; and protein, 0.18 per cent.

On October 25 abdominal reflexes were readily obtained; plantar responses were flexor; knee-jerks could not be elicited. The blood-urea was 37 mg. per 100 c.c. On October 26 the patient was still drowsy and after examination curled up and went to sleep. The left knee-jerk was obtained with difficulty. The urine contained albumin and acetone.

On October 28 the boy again complained of headache; examination of the nervous system revealed no abnormal physical signs. On 29th headache had disappeared and on 30th the condition of the urine was normal.

Progress hereafter was uneventful and the patient was discharged from hospital in apparently normal health on November 28. Cerebrospinal fluid withdrawn on November 9 contained no organisms, 7 cells per c.mm., all small lymphocytes; sugar, 55 mgm. per 100 c.c.; chlorides, 737 mgm. per 100 c.c.; and protein, 0·05 per cent. The Nonne-Apelt test was negative.

An acute toxic or hæmorrhagic encephalitis may occur in the course of focal or general pyogenic infection (Brain, 1928), or during an attack of a specific fever, especially measles and scarlet fever; sometimes the nature and source of the toxæmia may be obscure (Brain, Hunter and Turnbull, 1929). The highest incidence of this type of encephalitis in the acute specific fevers is among severe cases, e.g., cases of hæmorrhagic measles, and symptoms commonly appear when toxæmia is at its height.

In this respect it differs from acute perivascular myelinoclasis, the incidence of which is not determined by the severity of the exanthem, and which usually manifests itself at the end of the first week of the primary illness when the patient has commenced convalescence.

During the last two years one of us (J. P. M.) has seen two patients in whom the onset of smallpox was marked in an unusual manner by nervous symptoms possibly due to such an acute toxic encephalitis. In each case symptoms were present during the toxæmic stage and disappeared rapidly as that phase of the illness passed; to the clinical state the term "meningismus" might have been applied. A description of one of these cases is given here. For details of the child's condition prior to admission to the smallpox hospital we are indebted to Dr. F. Young.

Case 10.—E. N., an unvaccinated girl aged 6, had suffered previously from measles. On February 23, 1930, she vomited, complained of headache, and appeared drowsy, and on 24th was admitted to a children's hospital. She could be roused only with difficulty. The neck was slightly rigid and Kernig's sign was present. The pupils reacted to light. The limbs were flaccid; tendon reflexes were sluggish but all were present except the right knee-jerk; plantar responses were extensor. No coagulum formed in the cerebrospinal fluid which contained 0·68 per cent. chlorides and 0·02 per cent. protein.

On February 25 the patient was more conscious but lay in a semiflexed attitude. Physical signs were unchanged. The blood contained 7,000 white cells per c.mm. The urine was free from abnormal constituents.

On February 26 a smallpox eruption began to appear, and the reflexes returned to their normal condition. On admission to the smallpox hospital later in the day the patient was still a little drowsy; otherwise, on examination of the nervous system, no abnormal physical signs were found.

On March 1 the girl still slept a good deal. She could stand unsupported, but appeared rather unstable and took a few steps apprehensively in a waddling fashion on a wide base. The eruption was modified and of type 5 (between 100 and 500 lesions on the face).

On March 4 the patient could stand and walk naturally. Later she developed keratitis, but otherwise subsequent progress was uneventful.

The following case is unique among the records of 15,000 patients admitted to the London smallpox hospitals between 1893 and 1927. This man suffered from an acute myelitis which, commencing on the fifth day of rash, involved the optic nerves and the medulla, and led to death four days later. Unfortunately there is no record of any post-mortem examination.

Case 11.—J. E., a man aged 46, had one small scar due to vaccination in infancy. On June 22, 1899, he developed symptoms which he described as

those of a violent cold. On June 25 a smallpox eruption began to appear, and on 28th the patient was admitted to hospital: the rash was vesicular and discrete, with hæmorrhagic areolæ around many of the lesions. The temperature was 100° F. and continued to rise until shortly before death it reached 104° F.

On June 29 the man was very excited and restless and felt that he could not keep still in bed. He complained of strange sensations in his legs and abdomen, which came on in paroxysms and caused much distress. He also complained of dimness of vision. The following notes were made on this day by the late Dr. T. F. Ricketts.

> "10 p.m. The patient's excited and restless condition was due to no mental change but consequent only on his sensations. The condition got worse up to 7 p.m., when the unendurable sensations in his legs recurred every minute or two. The patient was partially collapsed, with small quick pulse, perspiring skin, &c. He was forced to sit up in bed with his legs drawn up, sweating and groaning. Every few minutes the exacerbation of sensation recurred and seemed to give unendurable distress. At these times he clasped or rubbed the seat of pain; in the intervals he seemed to have uneasy sensations elsewhere, generally in the abdomen, sometimes in the back. The patient would never call the sensation "pain"; he referred to it as "numbness," "cramps," "tingling," but seemed satisfied with no epithet. During the paroxysms and in the intervals, the muscles of the part affected were quite relaxed. The part affected was sometimes the left calf, sometimes the dorsum of the left foot, sometimes the other leg. The arteries of the legs and feet beat normally at all times and were equal in the two legs. There is no anæsthesia. Dimness of vision has increased. When first seen (about 3.30 p.m) there was an indistinct perception of objects, so that he could distinguish where a person was standing but could not count fingers held in front of his eyes. There was no hemianopia, but incomplete amaurosis equal in the two eyes. This became worse, and at 7 p.m. he was totally blind and had no perception of light and darkness. Eye reflexes tested at 3 p.m.; pupils dilated; slight sympathetic pupil reflex; no proper reaction to light, in fact when the eyes were closed the pupils contracted slightly and on opening the eyes they slightly dilated and oscillated a little; in consequence of the defective vision the convergence test could not be made. At 10 p.m. there was slight ptosis of the right lid (not noted before). Ocular movements were then examined. The patient when told to move his eyes in a given direction, moved his head, and when his head was held the eyes moved slowly to the required limits, but upward and downward movements were distinctly defective in extent. When moving the eyes to the right or left there was slight external strabismus at the limit of movement. The left eye was examined and the retina was normal; there was optic neuritis, redness and blurring of the disc, but no tortuosity of the vessels and no perceptible swelling. In consequence of the ptosis of the right

eye and the defective movement, the right disc could not be seen, but the lower part of the retina was normal."

On July 1 the patient was clear-headed and in no pain. Examination of the chest revealed nothing abnormal except an area of impaired resonance at the right base. Inspiration was laboured, the muscles of extraordinary respiration being brought into play, and there was some difficulty in swallowing. In the evening respiratory distress was more marked and cyanosis was evident. It was then found that the patient had no power to move his legs, neither could he feel them; only when attended to could he "feel his legs numb." Retention of urine and incontinence of fæces were present.

On July 2 the man's condition was worse, and he died early on the morning of July 3.

General Remarks on Recorded Cases.

We have no definite information of the true nature and pathology of the nervous condition in Case 11. It occurred as an isolated case among many thousands of patients suffering from smallpox, and the symptomatology differed from that presented by the cases of acute perivascular myelinoclasis observed recently; the time of onset in relation to the attack of the exanthem was within the limits of the "incubation period" of such cases. More particularly on account of the involvement of the optic nerves this case invites comparison with others recorded under the title of neuroptico-myelitis or Devic's disease.

Case 10 is not considered to bear any relationship to the remainder of the series. From evidence afforded by the symptomatology, and from the fact that the condition appeared during the toxæmic stage of smallpox, it is suggested that it might be assigned to the toxic encephalitis group, which, naturally enough, is but rarely encountered among cases of modified smallpox (two examples among 11,000 cases in our series).

Case 9 almost certainly represents a mild attack of acute perivascular myelinoclasis, but since in the intensity of its manifestations it differed so markedly from the typical cases, with regard to statistics, &c., it has been considered separately.

The significance of the group of cases of which Case 8 is quoted as an example is admittedly questionable. Nevertheless, the facts we have already mentioned, and particularly the temporal association of these cases with the typical disease, suggest the possibility that abortive cases of acute perivascular myelinoclasis may occur.

Cases 1 to 7 form a homogeneous group, of which the three fatal cases exhibited histological changes typical of acute perivascular myelinoclasis. The remaining four suffered severely, but recovered more

or less completely; in two of these symptoms were predominantly spinal. The average age of the patients attacked was 12 years, with extremes of 7 and 21; five were males and two were females. The period elapsing between the commencement of the outcrop of the focal rash and the onset of nervous symptoms varied between five and thirteen days, with an average of slightly more than seven days.

All patients in this series suffered from modified smallpox; this modification was due primarily to the benign nature of the strain of causative virus. With the exception of the third patient, who suffered from concurrent vaccinia and variola, all were unvaccinated.

In no instance was there evidence of case-to-case spread of the nervous condition, which never affected more than one member of a variolous family; each case appeared to arise spontaneously, though more or less contemporaneously with others.

Six cases occurred between the beginning of September, 1929, and the end of April, 1930. One of these was at Stoke-on-Trent, and five were drawn from London boroughs, mainly in the East End, where at that time smallpox was rife. Two of the London cases occurred in January, 1930, and two in February; three of these, two almost simultaneously, occurred in one particular hospital ward. Finally, one case occurred in April, 1931, and came from a London borough.

TABLE I.

Date	London Smallpox Hospitals		Remarks
	Cases of S.P. admitted	Cases of A.P.M.	
1928	290	0	
1929—			
1st quarter ..	279	0	
2nd ,, ..	1,020	0	Troup and Hurst's case occurred at Willesden in June
3rd ,, ..	602	1	Occurred in September
4th ,, ..	1,173	1*	Occurred in October
1930—			
1st quarter ..	2,623	4	Two in January; two in February at two days' interval in one ward
2nd ,, ..	2,189	0	Stoke case (No. 7) occurred in April
3rd ,, ..	671	0	
4th ,, ..	750	0	
1931—			
1st quarter ..	874	0	
2nd ,, ..	739	1	Occurred in April
3rd ,, ..	198	0	

* Mild case (No. 9).

TABLE II.

Year	England and Wales		
	Cases of S.P.	Deaths	Cases of A.P.M.
1928	12,420	53	0
1929	10,967	39	*3 ; 1 fatal
1930	11,839	28	5 ; 2 fatal
1931 (to Sept. 30) ..	5,028 (to June 30)	8	1 fatal
	40,254	128	9 ; 4 fatal

* Including one mild case (No. 9 in this paper).

TABLE III.

Date	England and Wales	
	Vaccinations* (with Govt. lymph)	Cases of A.P.M.
1922-1927	—	93 (including suspected cases)
1928—		
1st quarter	162,579	19
2nd ,, ...	145,898	28
3rd ,, ...	75,335	4
4th ,, ...	65,788	4
1929—		
1st quarter	60,068	4
2nd ,, ...	170,313	13
3rd ,, ...	61,434	8
4th ,, ...	60,457	2
1930—		
1st quarter	85,630	4
2nd ,, ...	74,079	1
3rd ,, ...	68,808	1
4th ,, ...	56,264	0
1931—		
1st quarter	Not available. Writer's personal estimate at roughly 200,000	1
2nd ,, ...		3
3rd ,, ...		1
	1,286,653	93

* An unknown percentage, probably about 30, of the total vaccinations in this country are performed by private practitioners using proprietary lymphs, so that the above figures represent about two-thirds of the real total; in 1929, however, the S.S. "Tuscania" scare was responsible for much extra private vaccination.

This chronology and the relation of the cases to the prevalence of smallpox are shown in Table I. If now comparison is made between, say, the incidence of smallpox during the first and second quarters of the year 1930, it is clear that the frequency of the nervous disease is

not related to that of the exanthem. In Table II we show the total number of smallpox cases notified in England and Wales during the same period, their mortality-rate, and the incidence of acute perivascular myelinoclasis in the country as a whole. Since all examples of the nervous condition, save the Stoke case, were drawn from the London area, the figures in Table I give an erroneous impression of its frequency. It may be interesting to add in Table III figures of the incidence of the post-vaccinal disease, which at present appears to be becoming increasingly infrequent; again the lack of direct relation between the number of vaccinations and the incidence of acute perivascular myelinoclasis is apparent. It is impossible to compare the relative incidence of the nervous condition after vaccination and after smallpox, for the majority of primary vaccinations are performed in infancy, an age-period almost, if not quite, free from acute perivascular myelinoclasis. But it is important to realize that discontinuation of vaccination would not necessarily lead to disappearance of acute perivascular myelinoclasis, were the predisposed individuals to acquire as a result an attack of smallpox.

Treatment with Convalescent Serum.

Horder (1929) successfully vaccinated a boy aged 4½ years, and at the same time successfully re-vaccinated the mother. On the eighth day the boy became drowsy, and on the eleventh day was stuporous. On the fifteenth day 5 c.c. of the mother's serum was injected intrathecally into the child, who subsequently made a good recovery.

Hekman (1930), with fourteen recoveries out of sixteen patients treated, and Grüneberg (1930), with two patients, both of whom recovered, have since claimed good results in the treatment of post-vaccinal encephalitis from the employment, mainly by the intravenous route, of the serum or citrated blood of convalescents from vaccinia. In one case the serum was obtained from a man vaccinated four years previously.

The publication of Horder's article suggested the use of smallpox convalescent serum on our variolous encephalitics, and as a supply of serum had already been collected from patients at about the fourth week of numerically severe attacks of modified smallpox, the first case (No. 3 in this paper) was so treated. (It will be remembered that this case suffered from concurrent variola and vaccinia and recovered.) Of the seven severe cases of acute perivascular myelinoclasis, four received serum in doses of from 10 to 22 c.c.; three, in one of which symptoms were predominantly spinal, recovered, and one died. Of the three not treated

with serum, one with predominantly spinal symptoms recovered and two died.

It is obvious that the number of cases in this series is too small for any far-reaching inference to be drawn therefrom. However, in attempting to assess the value of any therapeutic measure in cases of this disease the following facts should be borne in mind: that, clinically at least, two types of the condition (encephalic and spinal) may be recognized; that the case mortality is definitely higher in the encephalic group; and that, in the absence of any "specific" treatment, it is possible to anticipate with a degree of confidence the recovery of a certain proportion of the cases.

If it could be shown that in a large number of cases of acute perivascular myelinoclasis of severe type the recovery rate was much higher among those receiving convalescent serum than among those not so treated, the theory postulating the direct responsibility of the virus of the exanthem for the nervous condition might hold a stronger position than it does. It cannot be said that this has yet been established. Those rejecting this theory can find on theoretical grounds scant support for a principle of treatment with antibodies specific only against the causative agent of the associated disease (vaccinia, variola, measles, &c.), especially when it is remembered that by the time nervous symptoms appear the patient must often already be in possession of such antibodies. On the other hand, similar treatment applied in the toxic encephalitis of, for example, measles, would be expected to yield good results (*vide* Lowenberg and Shaller, 1926). On theoretical grounds it seems possible that, if acute perivascular myelinoclasis is actually an infection, the serum of recovered cases might be employed with advantage if it were at all certain that the donors were free from the causative agent of the condition.

Note on the Pathology and Cerebrospinal Fluid.

We have but few remarks to make on the pathology. In all three fatal cases the lesions were typical of acute perivascular myelinoclasis and were indistinguishable from those in cases following vaccination, of which one of us (E. W. H.) has examined more than a dozen. Only the condition of the lumbar cord in Case 1 is worthy of special mention; here many of the anterior horn cells were necrotic, a distinctly unusual occurrence in the disease under consideration. While, when situated in an area of dense infiltration, the nerve-cells may exhibit mild degeneration, the above-mentioned observation is in our experience without

parallel, though in Troup and Hurst's case the lumbar cord was, at autopsy, in a diffluent state and, had examination been possible, would presumably have shown destruction of nerve-cells.

The laboratory reports on the cerebrospinal fluid, for which we are indebted to Dr. V. D. Allison, supply some interesting information. The early phases of the disease are marked by a moderate or pronounced pleocytosis; the cells may either be wholly lymphocytic (Cases 2 and 9), or they may include a high percentage of polymorphonuclear leucocytes. In the course of a few days the cell-count rapidly falls and mononuclears alone are found. Except in Case 6, the total protein was moderately increased; it did not always fall with diminished cell-content of the fluid, and in Case 2 even showed a rise as late as the sixteenth day. The Nonne-Apelt reaction was invariably negative. The amount of glucose probably showed no significant alteration from the normal (variously given as 45 to 85 mgm. per cent.), though in Cases 5 and 6 the figures were rather high. In Cases 2, 6 and 9, chlorides, estimated as NaCl, were apparently diminished during the early stages; in Case 5, on the other hand, abnormally high figures were obtained on the ninth and seventeenth days. The results of the examinations are set forth in Table IV.

TABLE IV.

		Examination of C.S.F.							
Case	Stage	Cells	Polys. %	Lymph. %	Large mono. %	Sugar mgm. %	Chlor. mgm. %	Protein %	Nonne-Apelt.
2	4 days ..	74		100		64	684	0·07	Neg.
	9 ,, ..	27		100		62	725	0·07	Neg.
	16 ,, ..	9		100		62	713	0·14	Neg.
3	2 days ..	483 R. 542 W.	43	53	4	60	749	0·08	Neg.
	6 ,, ..		22	74	4			0·10	Neg.
4	3 days ..	358 R. 112 W.	1	96	3	80	743	0·10	Neg.
	9 ,, ..	102 R. 29 W.		100		66	731	0·035	Neg.
5	2 days ..	490	87	8	5	85	743	0·076	Neg.
	9 ,, ..	42		91	9	95	778	0·085	Neg.
	17 ,, ..	12		100		90	760	0·060	Neg.
6	2 days ..	36	30	64	6	95	702	0·02	
9	3 days ..	58		100		58	708	0·18	
	19 ,, ..	7		100		55	737	0·05	Neg

Several patients suffered from albuminuria at a time when no pus was present in the urine, and, in all three cases in which the urea content of the blood was determined, the figure considering the age of the individual was distinctly higher than normal. In fatal cases no renal lesions were detected.

Discussion.

Acute perivascular myelinoclasis possesses a more or less characteristic symptomatology. Although morbid changes are usually widespread, from a clinical standpoint two types of the condition may be recognized, according to the relative intensity of encephalic or spinal symptoms. From a comparative study of the reports of the Vaccination Committee (1928, 1931) and of the literature on cases following smallpox, it seems that among post-vaccinal cases the first type may predominate, while in association with smallpox spinal symptoms are more commonly encountered. Yet even clinically the two types often overlap at some stage and the distinction is rarely clear-cut, though from a prognostic point of view it may have some significance. Even when encephalic symptoms are least prominent and the clinical features suggest a major incidence upon the lumbar region of the cord, some degree of drowsiness is rarely wholly lacking; this was true even of Troup and Hurst's case which, belonging chronologically to the recent outbreak, was both clinically and histologically the most purely myelitic of those occurring during the present decade. In either type the onset of the nervous state, if not sudden, is never insidious, and it follows the primary disease at a characteristic and relatively fixed interval, from ten to thirteen days in the case of vaccination (i.e., between the seventh and tenth days of the course of the vaccinial lesion), from five to thirteen days after the appearance of the focal rash of smallpox, at about the end of the first week in measles, during the second half of antirabic treatment, &c. This similarly of incubation periods is remarkable.

Frequently attention is drawn to the onset more by observation of something unusual in the state or behaviour of the patient than by any complaint on his part. An unsteady gait or unnatural somnolence may arouse suspicion. A rise in temperature from a normal or subnormal level seems the rule, and this fever, usually remittent, persists throughout the acute stages; headache with pain in the back or limbs is a common symptom, and the patient may vomit. In either type of the malady drowsiness is usually soon the outstanding feature, but sometimes irritability may occur. Neck rigidity, Kernig's sign, and tache

cérébrale may be present. The initial condition of the tendon reflexes is not constant; the abdominal reflexes usually disappear early. Disturbances of sphincter control are almost constantly present. In the encephalic type the drowsy state deepens to a stupor from which the patient cannot be roused, and later perhaps to profound coma; the limbs typically become flaccid and the reflexes are abolished, though a condition of clasp-knife rigidity may obtain, more especially in the upper extremities. The plantar responses either cannot be elicited or are of the extensor type. Collective rather than individual paralyses may be present, as paraplegia, pareses of the upper limbs, or facial weakness on one side. Ocular changes are not often found, though there may be temporary inequality of the pupils and intermittent squints; papilloedema had been recorded. Trismus may be extreme, and in the past has been attributed to tetanus; changes in the region of the fifth nucleus may explain this spasm. Sweating about the head and excessive salivation, either real or apparent from dysphagia, may be prominent. This state may in a very few days terminate in death with signs of bulbar involvement and terminal hyperpyrexia; or on the other hand, an apparently moribund patient may make a most unexpected and dramatic recovery. Before death signs of broncho-pneumonia are often present.

If the patient survives the acute stages, the unconscious state may last for days or even weeks. Bed-sores and cystitis are likely to supervene, and together with broncho-pneumonia may lead to death. Our own experience suggests that certain of the "bed-sores" arise as trophic lesions on parts of the body related to the most severely affected regions of the spinal cord; such lesions, appearing first as bullæ, occur early, and their presence on the foot or lower leg (not necessarily over "pressure points") is too likely to be regarded as a result of that undesirable combination, an unconscious patient, a hot-water bottle and a careless nurse.

In the spinal type (e.g., Cases 2 and 4) the patient, at the end of a period which can be measured in days, has lost all signs of drowsiness; in the encephalic type the return of consciousness may be so gradual as to make it doubtful at times whether the patient has regained understanding or not. Certainly at a somewhat later stage his immobility and unresponsive state may be attributed more to a peculiarly inert state of mind than to a lack of appreciation of his environment.

True urinary incontinence may precede return of consciousness, and in paraplegic cases rectal and vesical sense are usually wanting when

the patient reaches a stage of intelligence. Urinary incontinence may commence as a constant dribble, become intermittent as the bladder functions reflexly, and disappear finally with gradual re-awakening of bladder sensibility and increasing voluntary sphincter control. Improvement in rectal and vesical sensibility may be slow, but it usually follows closely upon recovery from paralysis in the lower limbs. Nevertheless a liability to transient, intermittent loss of sphincter control constitutes one of the legacies of the disease.

With the return of consciousness the distribution of paralysis can be determined with greater accuracy. Flaccid paralyses with absent reflexes are usual; the abdominal reflexes can rarely be obtained; plantar responses are absent or of the flexor type. Most commonly at this time the cranial nerves are normal, though trismus, facial weakness or strabismus may persist for a while. In the upper limbs, weakness and inco-ordination are more usual than complete paralysis. Return of function is not long delayed, and as power is regained spasticity may develop. Deformities of muscular origin, particularly in the lower limbs, and evidence of muscular inco-ordination may enlarge the clinical picture.

In the majority of instances, after a period of weeks or months according to the severity of the initial paralysis, recovery is almost complete, but in the spinal type some spastic weakness of the lower extremities may remain; moreover, muscular deformities of the limbs may recur later (*vide* Case 2).

Some sensory loss commonly accompanies the motor disturbances and may take the form of complete anæsthesia over the paralysed area, in certain cases affecting those parts of the body below the nipple level, or may be incomplete or dissociated. At the onset of nervous illness, hyperæsthesia may be detected just above the level of apparent maximal involvement of the cord, and pain, sometimes severe, may be experienced in the head, back or limbs. Pain may recur, especially in the extremities, immediately prior to return of motor function. The discrimination between hot and cold is usually regained last, but recovery from sensory disturbances precedes that from motor paralysis.

On the mental side, the duration of somnolence varies much from case to case (seven to fourteen days in our series). The return of speech may be delayed, and though clearly understanding remarks addressed to him the patient may for a time be unable to reply coherently. This dysarthria is probably due to imperfect co-ordination of muscles concerned in the act of talking. In our series this phenomenon was most marked

in Case 5, but it differed considerably in detail from the disturbances of speech described by the older writers. An emotional stage is quite common, but more striking mental derangement may be seen in the early days of convalescence. Delusions, abnormal behaviour and moral perversions are features of this phase, during which functional manifestations may be superimposed upon earlier organic lesions. In our experience this stage has been short-lived (*vide* Cases 4 and 5), and in none of the recovered cases has there been permanent mental abnormality.

These then are the symptoms of acute perivascular myelinoclasis, whether occurring in the course of smallpox, vaccinia or measles (Wohlwill, 1928; Greenfield, 1929). Greenfield concluded that "no clinical or pathological distinction can be drawn between the encephalomyelitis following measles, and that which may follow vaccination and smallpox"; and no one reading the remarks introductory to his clinical description can fail to agree that many of them would form an equally fitting preface to our own cases, while, as already stated, we have been unable to detect any histological differences between the cases following vaccination and the present series following smallpox.

Owing to their almost invariably favourable course, the nature of the nervous complications of varicella, rubella and mumps is less clear. Clinically, many of the cases arising after varicella have shown predominant affection of the cerebellum, and in the sole fatal case of this type examined histologically (van Bogaert, 1930), lesions, though more marked in the white than in the grey matter, do not appear to have been those of acute perivascular myelinoclasis. Zimmerman and Yannet (1931), however, in a child with fever, irritability and convulsions beginning three days after appearance of the rash, described diffuse non-characteristic degeneration of ganglion cells, and perivascular destruction of the myelin sheaths in the parietal and occipital white matter. The clinical features of the cases following rubella recorded by Bénard (1921) and Brock (1929) suggested acute perivascular myelinoclasis, but histological proof was lacking.

The position of the so-called paralytic accidents of antirabic treatment is also confused, since, as Hurst (1932) has pointed out, various observers have not always been at pains to distinguish two very different conditions. On the one hand there are cases of true street-rabies developing in spite of treatment, and rare cases where the *virus fixe* has proved pathogenic for man (França, 1910; Busson, 1926); on the other hand, the residuum are undoubtedly examples of acute perivascul a

myelinoclasis. Bassoe and Grinker (1930) and Stuart and Krikorian (1930) have recently described such cases; the case of Fielder (1916) was certainly, and that of Babes and Mironesco (1908) probably, similar.

If, therefore, we find the same clinical and pathological condition following after a roughly similar "incubation period," such different predisposing causes as smallpox, measles, antirabic treatment, &c., the conclusion seems inevitable that we are dealing with an independent malady activated by the conditions mentioned, and not with one resultant upon some change in virulence or other property of the virus of the primary affection. In particular, it is difficult to envisage what modification of the virus of rabies, which always produces the polioclastic type of inflammation with major incidence upon the grey matter, destruction of nerve-cells and the development of characteristic inclusions, could make it responsible for an encephalopathy characterized by a primary destruction of the myelin sheaths and but little alteration in the nerve-cells which do not contain Negri bodies. Or, again, that the virus of vaccinia, which is not in the strict sense of the term neurotropic, but which gives rise to lesions primarily meningeal (Hurst and Fairbrother, 1930), can, after some hypothetical modification involving no change in its other pathogenic properties, produce lesions which from the neuropathological aspect are the very antithesis of those of "cerebral vaccinia."

But another, and to our minds still more weighty, objection to the theory of "direct causation" depends on the periodicity of these visitations of nervous disease. Acute perivascular myelinoclasis is no new malady and, judging by the numerous accounts published, cases following smallpox were relatively frequent in the closing decades of the nineteenth century; after Aldrich's paper in 1904, however, with the sole exception of Eichorst's case in 1913, no mention of the condition seems to have been made in the literature until McIntosh's note of 1928. Of course, during much of the present century smallpox was an uncommon disease in this country, but the same argument does not apply in the case of vaccinia. It seems likely that "post-vaccinal encephalitis" was first seen by Comby in 1907, and Turnbull and McIntosh's first case occurred in 1912, yet the recent outbreak is unprecedented. The fact that the condition has lately again become infrequent is fully in accordance with the known behaviour of acute perivascular myelinoclasis, and for this reason can certainly not be ascribed solely to the efforts, however soundly based, which have been aimed at the prevention of the condition.

Koritschoner and Schweinburg (1925), dealing with the statistics of antirabic inoculation at the Vienna Institute, state that between 1894 and 1914, 7,632 cases were treated without accident, while between 1915 and 1923, 6,764 cases showed 39 paralytic accidents. Greenfield (1929) stresses a similar periodicity in the case of the disease following measles, and of other encephalopathies presenting a somewhat similar histological picture, e.g., neuroptico-myelitis. Our own views are exactly expressed in the ensuing extract from his article: "A condition which occurs in so small a proportion of cases of measles, and which in one year may suddenly appear with much greater frequency and cause more deaths than in the previous twenty years, is unlikely to be due to a sudden change in the nature of so common a disease. It is much more likely to be due to some other concurrent epidemic which does not produce much obvious effect unless the carrier of the virus is attacked by smallpox or measles." We would merely emphasize the still greater improbability of a similar change in pathogenic properties occurring simultaneously in at least three different viruses, viz., those of smallpox, vaccinia and measles.

If, on the other hand, the virus of the exanthem plays merely an indirect rôle, it is possible that acute perivascular myelinoclasis may from time to time occur as an independent disease. What evidence is there to support this?

Turnbull (1928) states that "there can be no doubt that a condition resembling post-vaccinal encephalitis has occurred independently of recent vaccination and observed exanthemata. Küssner and Brosin (1886) described accurately identical changes in the cord of a man who had suffered for a year from chronic gonorrhœa. The changes observed in the cord in the first case of Francotte (1890) appear to be similar, whilst Krabbe (1913) described the changes in the brain. Very similar but more chronic changes were described by Dreschfeld (1894). Wohwill (1928) said that he had observed changes identical with those of post-vaccinal encephalitis in a patient who was not suffering from any known infectious disease."

Greenfield (1930) recorded two cases identical with those following vaccination, &c., occurring after "influenza." In the second case, however, it seems highly probable that the influenzal symptoms represented merely the febrile onset of the nervous condition, a view with which McAlpine (1931) concurs.

During the last few years numerous observers have noted a general increase in the incidence of what is termed acute disseminated encephalo-

myelitis, and many clinical accounts have been published, e.g., those of Redlich (1927), Pette (1927), Martin (1928), Flatau (1929), Spiller (1929), van Bogaert and Baeten (1930), McAlpine (1931), &c. It is not certain that all these cases have belonged to the type of disease at present under discussion; but few pathological accounts are available, and while Paul (1928) thought the condition in his cases similar to that in "post-vaccinal encephalitis," Pette (1928), Cournand (1930) and Dagnélie and van Bogaert (1931) have described lesions more closely resembling those of "acute disseminated sclerosis," which condition we would prefer to designate "acute focal myelinoclasis." The cases of Brain, Hunter and Turnbull (1929) do not, either clinically or pathologically, tally entirely with either of these groups.

The work of Grinker and Bassoe (1931) makes it likely that we have to separate a number of closely-related but distinct morbid entities, for while their first case exhibited a histological picture identical with that of "post-vaccinal encephalitis," their second case resembled more closely the so-called "acute disseminated sclerosis," and their third case was again different from either. They state that if a pathological classification of infections of the central nervous system on the basis of distinct, regularly occurring microscopical changes were proposed, each group would embrace examples of more than one clinical syndrome. Excluding cases of syphilis, parasitic infections and sepsis, the distinguishing features of the various groups might be as follows:—

(1) Severe focal demyelination, less severe axonal change, microgliosis, mild or absent perivascular infiltration, gliosis—disseminated sclerosis and some cases of acute disseminated sclerosis.

(2) Focal incomplete or complete softenings, not perivascular, microgliosis, variable lymphocytic infiltration, vascular and connective-tissue proliferation—acute disseminated encephalo-myelitis and acute disseminated sclerosis.

(3) Focal incomplete perivascular softening involving the whole nerve-fibre, coalescence of lesions, microgliosis, mild lymphocytic reaction, secondary gliosis—post-vaccinal encephalitis, &c., and disseminated encephalo-myelitis.

(4) Diffuse subcortical destruction of nerve-fibres, probably primary in the myelin, mild or absent lymphocytic infiltration, primary progressive gliosis with secondary regressive glial forms, connective-tissue scar—Schilder's encephalitis and disseminated encephalo-myelitis.

(5) Diffuse but relatively selective ganglion-cell destruction, abundant perivascular and tissue lymphocytic reaction, mild micro-

gliosis, white matter spared—rabies, encephalitis lethargica and poliomyelitis.

(6) Hyperplastic meningeal reaction, regressive changes in capillary endothelium, formation of new blood-vessels, degenerative changes in nerve-cells, absent mesodermal infiltrations—toxic encephalitis in the acute infections, lead poisoning, &c.

It seems fair to conclude, therefore, that acute perivascular myelinoclasis may occur independently of any exanthem, and is entitled to recognition as an independent clinical and pathological entity; the application of a single comprehensive term to all cases, whatever the predisposing malady, is the logical development of this knowledge. It is clear, moreover, that different authors have described as disseminated encephalo-myelitis rather widely differing pathological conditions, and until the present confusion regarding disseminated encephalo-myelitis, acute disseminated sclerosis, &c., has been dispelled, in the absence of any definite knowledge of their ætiology, it seems desirable to classify this group of obviously related diseases on a histological basis. For the time being, then, nomenclature will depend on distinctive histological features, and this principle has been followed in the present paper.

Finally, whatever the exact relationship between acute perivascular myelinoclasis and acute focal myelinoclasis, and between the latter and disseminated sclerosis, these diseases are in certain features sufficiently similar to suggest the wisdom of considering the ætiology of the group rather than that of the individual malady.

In the case of acute perivascular myelinoclasis the discovery of a filterable virus has been eagerly awaited. The grouping of cases in certain districts, the occasional affliction of more than one member of a family,[1] the periodicity of the disease, the febrile onset of symptoms, suggest an infectious origin, yet it must be remembered that such evidence is not necessarily conclusive and that other factors may recur at intervals and affect only a certain proportion of individuals; as a rather remote analogy we might quote the outbreaks of lathyrism in India.

Experimental work has told us very little, and that only of a negative character. All our own attempts to reproduce the condition by intracerebral inoculation, combined on occasion with skin vaccination, of

[1] The case of dissimilar twins who, vaccinated on the same day, both developed "post-vaccinal encephalitis" and died on successive days recently attracted considerable notice in Parliament and in the press. Histological examination was performed by one of us. (E.W. H.).

monkeys and rabbits with brain emulsions from cases following vaccinia and smallpox have been fruitless, as have those of other workers. Cournand obtained similar negative results in monkeys and rabbits with the brains of two of his spontaneous cases showing the focal type of lesions ("acute disseminated sclerosis"), while the "spherula insularis" as the causative organism of disseminated sclerosis is now generally discredited. Although as a rare event vaccine virus has been isolated from the brains of the post-vaccinal cases, this observation has no ætiological significance, as general dissemination of the virus normally follows vaccination; it has already been stated that the lesions produced in the nervous system by the vaccine virus are totally different from those of acute perivascular myelinoclasis.

Though perhaps of little import, it is a fact that in all the (now numerous) neurotropic virus diseases of man and animals, the brains exhibit what Schroeder (1925) has called the polioclastic type of inflammation, that is to say, that the primary attack is on the grey matter, while of the myelinoclastic diseases characterized by a primary affection of the myelin sheaths, not one has yet been shown to result from the action of a virus. While the long-disputed question as to whether the lesions of disseminated sclerosis are primarily inflammatory or not has, apparently, recently almost always been answered in the positive, we do not believe that this conclusion necessarily follows from the evidence available. In the purely degenerative lesion resulting from the aseptic occlusion of a cerebral blood-vessel, the products of nervous disintegration may excite very lively inflammatory phenomena. Some of the disintegration products of myelin, and in particular cholesterol, are powerful tissue irritants, and the variable inflammatory manifestations in acute perivascular myelinoclasis could conceivably be explained as due to their action. Further, the demyelination in acute perivascular myelinoclasis apparently occurs suddenly and with great rapidity, and in cases fatal some time from the onset there is no indication that after the first few hours the lesions progress; this would probably be in keeping more with a sudden attack on the myelin sheath by a toxin or enzyme than with that of a living organism. There is, of course, the possibility that the condition is the result of an infection, but that the nervous changes are conditioned by some product of that infection and are not due to a direct attack of the infective agent itself.

It is of interest that in disseminated sclerosis Brickner (1930, 1931) has obtained evidence that the blood-serum shows myelin-destroying properties not possessed by normal serum. His results were not due to an

excessive amount of normal lipase or to decreased anti-lipase activity, as tests indicated a difference in properties between the normal lipolytic agent and that of disseminated sclerosis. In our own experiments, using an active preparation of pancreatic lipase, we demonstrated that *in vitro* the amount of acid produced after incubation with brain-emulsion was roughly the mean of that produced by the same preparation using olive-oil as substrate on the one hand, and ethyl butyrate as substrate on the other. But on intracerebral or intrathecal inoculation no lesions analogous to those of any of the demyelinating diseases developed; intravenous inoculation into monkeys suffering from poliomyelitis or cerebral vaccinia, in which it might reasonably be supposed that vascular and meningeal permeability was greater than normal, was also ineffective. It must, of course, be remembered that a lipase, or rather an esterase, has been demonstrated in small amounts in normal nervous tissues (Quinan, 1916), and, presumably, must be kept in check by anti-lipase activity. It is just conceivable that local removal of the inhibitory factor might result in demyelination in the area concerned.

While these concluding remarks are purely speculative, in the absence of fact speculation may promote an unbiased approach to a problem and lead to solution along what appear at first improbable lines. If, as appears likely, the demyelinating maladies we have mentioned are ætiologically more or less closely related, it would seem that acute perivascular myelinoclasis, as the most acute representative of the group, would offer the most favourable field for research.

Conclusions.

Acute perivascular myelinoclasis is a definite clinical and pathological entity with a more or less characteristic symptomatology and a highly characteristic histology.

It may occur independently of any recognized exciting factor, or it may follow certain exanthemata, smallpox, vaccinia, measles, varicella, and probably rubella. It may also occur during the course of antirabic treatment.

The ætiology is unknown but may be connected with that of acute focal myelinoclasis ("acute disseminated encephalo-myelitis," "acute disseminated sclerosis") and of disseminated sclerosis.

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A NOTE ON THE RESULT WHICH FOLLOWS THE GRAFTING OF THE RAW PERIPHERAL END OF THE DIVIDED CERVICAL SYMPATHETIC NERVE TO ANOTHER NERVE IN THE VICINITY.[1]

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DURING the progress of a research designed to determine the effect of anastomosing the central end of the divided cervical sympathetic nerve to the peripheral end of certain divided motor nerves of the neck, the opportunity arose of observing the results which follow:—

(*a*) The anastomosis of the peripheral end of the divided cervical sympathetic to some other neighbouring nerve.

(*b*) The leaving of the peripheral end of the divided cervical sympathetic nerve without surgical union with any other nerve.

The prominent signs caused by division of the cervical sympathetic nerve in the cat are, enophthalmos, small pupil, prominence of the nictitating membrane, and drooping of the whisker hairs. All these signs and symptoms disappear on Faradic stimulation of the peripheral end of the divided cervical sympathetic nerve. Other signs, as the dilatation of the arteries of the pinna and the absence of sweating of the skin of the face on the side of operation, were ignored. It was thought that the four signs chosen for observation would suffice to indicate by their disappearance, or by their persistence, the recovery or lack of recovery of the ocular signs caused by section of the cervical sympathetic.

The operations were made on 46 cats and 2 Rhesus monkeys. A few of the cats died of some known or unknown malady, a few were killed by chloroform, and a few have been too recently operated on for a judgment to be reached as to the final condition of their ocular signs. A sufficient number—28—of the experimental animals remain for a definite conclusion to be formed as to the value of suturing the peripheral end of the divided cervical sympathetic nerve to another nerve.

It is known that in man, when the cervical sympathetic has been

[1] The research on which this paper is founded is much indebted to the generous support of the Carnegie Corporation, of the Milbank Memorial Foundation, of the Lillian Babbitt Hyde Foundation, and of several private friends.

severed, occasionally after a more or less long time the ocular signs disappear. It may be presumed that in such a case the raw peripheral end of the sympathetic becomes adherent to, and later is in functional union with, some neighbouring nerve. It is not possible to ascertain the percentage of recoveries in man. The conditions for which in surgery the cervical sympathetic is divided are so serious (cardiac pain, Raynaud's disease, &c.) that the surgeon's mind is concentrated on the relief given to the serious symptoms from which the patient is suffering, and the ocular signs in comparison seem to be but a trivial incident in the case.

We were not altogether surprised at the results of our experiments. Langley and Anderson [4], in 1904, anastomosed the central end of the 5th cervical nerve to the peripheral end of the cervical sympathetic nerve. The effects of stimulation of the 5th cervical nerve some time later showed clearly that functional union had taken place, for all the normal effects of stimulation of the cervical sympathetic nerve were observed.

One of us (B) [1] performed an experiment on a cat (August, 1927), which confirmed and extended the results obtained by Langley. The central end of the divided cervico-facial division of the facial nerve was united to the peripheral end of the divided cervical sympathetic nerve. At the end of six months there was no enophthalmos, and no prominence of the nictitating membrane; the pupil was not small, but was not quite so large as the opposite or normal pupil, and the whisker hairs on the side of the operation no longer drooped, but stood out like those of the opposite side.

Cannon [2] united the phrenic nerve in cats low down in the neck to the cervical sympathetic. Rhythmic efferent impulses associated with respiration passed along the sympathetic, presumably to the thyroid, and provoked excitability, rapid pulse, increased metabolism and other symptoms which were interpreted as evidence of experimental hyperthyroidism. Horrax [3] repeated these experiments and confirmed Cannon's conclusions.

Syllabus of Experiments.

A. The main operation was cervical sympathetic-hypoglossal anastomosis (right side).

The secondary operation was hypoglossal-cervical sympathetic anastomosis (right side).

1. *CAT.*—226 days. No enophthalmos, pupils equal, whiskers of both sides at same level. Right nictitating membrane shows slightly.

2. *CAT.*—No secondary anastomosis performed.

86 days. All signs of cervical sympathetic division well marked.

Cat anæsthetized.—Faradism: electrode was placed on the skin ¼ in. behind and above the right angle of mouth—the eyeball advanced, the pupil enlarged and the nictitating membrane disappeared. The Faradism at this spot was continued for some little time with interruptions. It was then noted that the stimulation caused both pupils to enlarge at the same time.

When the cat had recovered from the ether anæsthesia there was no difference between the eyes; the ocular signs on the right side had disappeared. Three and a half months later complete recovery of the right ocular signs was maintained.

The explanation seems to be that at the time of Faradic stimulation, 86 days after the severance of the cervical sympathetic, its peripheral end had become grafted on to another neighbouring nerve, and that the Faradism overcame the obstruction at the point of anastomosis which had up to the moment of Faradism prevented the passage of nerve impulses.

3. *CAT.*—70 days. No difference between the eyes. Two months later same report.

4. *CAT.*—70 days. No difference between the eyes.

5. *CAT.*—No secondary anastomosis performed.

323 days. No recovery of the ocular signs, but perhaps they are not so noticeable as at first.

6. *CAT.*—No secondary anastomosis performed.

178 days. No change whatever in the ocular signs.

7. *RHESUS MONKEY.* No secondary anastomosis performed.

180 days. No change in the ocular signs.

B. The main operation was cervical sympathetic-facial anastomosis (right side). In the experiments no secondary anastomosis was done.

8. *CAT.*—No secondary operation performed.

Death on the thirty-fifth day. No change in the ocular signs.

9. *CAT.*—No secondary anastomosis performed.

51 days. On placing the electrode above and behind angle of mouth: eyeball moved forwards, pupil dilated, membrana nictitans disappeared.

These were only temporary results of the stimulation. The ocular signs were as marked after the stimulation as before. Four months later there was no amelioration of the ocular signs.

10. *CAT.*—No secondary anastomosis performed.

70 days. Ocular signs typical.

11. *CAT.*—No secondary anastomosis performed.

172 days. There is no enophthalmos, the right eyeball is more prominent than the left, but the right pupil is small, the nictitating membrane prominent and the whiskers droop. Presumably the fibres in the peripheral end of the divided cervical sympathetic which innervate the muscle of Müller have become functionally attached to some other nerve, but why there is exophthalmos cannot be explained so easily.

12. *CAT.*—No secondary anastomosis performed.

231 days. Ocular signs entirely unchanged.

13. *CAT.*—No secondary anastomosis performed.

230 days. Ocular signs quite unchanged.

14. *RHESUS MONKEY.*—No secondary anastomosis performed.

125 days. Ocular signs present but seem to be less noticeable than formerly.

C. The main operation was cervical sympathetic-superior laryngeal anastomosis (right side).

The secondary anastomosis was superior laryngeal-cervical sympathetic anastomosis (right side).

15. *CAT.*—30 days. No change in the ocular signs.

16. *CAT.*—155 days. Complete recovery—both eyes entirely alike.

D. The main operation was anastomosis of the cervical sympathetic with the motor portion of superior laryngeal nerve (right side).

The secondary operation was anastomosis of the motor portion of superior laryngeal nerve with the cervical sympathetic (right side).

17. *CAT.*—100 days. Pupils equal: no enophthalmos; membrana nictitans still shows a little.

18. *CAT.*—In this experiment the secondary operation was hypoglossal-cervical sympathetic side-to-end anastomosis. This was found more convenient than using the central end of the motor part of the superior laryngeal nerve which is a very small nerve.

Notes made on 96th day and 226th day: ocular signs completely disappeared.

19. *CAT.*—155 days. No difference between the two eyes. The secondary anastomosis in this experiment was of the superior laryngeal nerve, with the cervical sympathetic, side to end.

E. The main operation was cervical sympathetic, descendens noni anastomosis (right side).

The secondary operation was descendens noni, cervical sympathetic anastomosis (right side).

20. *CAT.*—196 days. Both eyes alike. Ocular signs completely disappeared.

F. The main operation was cervical sympathetic, phrenic anastomosis.
The secondary operation consisted of grafting the peripheral end of the cervical sympathetic to (*a*) the central end of the phrenic end to end, or (*b*) to the anterior primary division of the 5th cervical nerve, end to side (right side).

21. *CAT.*—The secondary anastomosis consisted of the grafting of the peripheral end of the cervical sympathetic on to the 5th cervical nerve. 168 days. Pupils equal; no enophthalmos; whiskers at same level on both sides; slight appearance of membrana nictitans.

22. *CAT.*—The secondary anastomosis consisted of the grafting of the peripheral end of the cervical sympathetic to the phrenic nerve, end to end. 172 days. Same result as in Cat 21.

G. The main operation was cervical sympathetic-recurrent laryngeal anastomosis.
The secondary anastomosis, the peripheral end of the cervical sympathetic was never grafted to the proximal end of the recurrent laryngeal.

23. *CAT.*—The secondary anastomosis was an end to side grafting of the peripheral end of the cervical sympathetic to the lower border of the hypoglossal. 60 days. No enophthalmos; other ocular signs have nearly disappeared.

24. *CAT.*—The secondary anastomosis was an end-to-side union of the peripheral end of the cervical sympathetic to the lower border of the superior laryngeal nerve. 53 days. Same result as in Cat 23.

25. *CAT.*—No secondary anastomosis.
90 days. No improvement in the ocular signs.

26. *CAT.*—No secondary anastomosis.
156 days. No improvement in the ocular signs whatever.

H. The main operation was cervical sympathetic-glossopharyngeal anastomosis. The whole glossopharyngeal or only its motor part was used in the experiment (right side).
No secondary anastomosis was carried out in either of the two experiments performed.

27. *CAT.*—The notes on the 95th and 231st days state that there is no improvement in the ocular signs.

28. *CAT.*—Died under ether on the 32nd day. There was no change in the ocular signs.

Analysis of Experiments.

The experiments were performed on Cats and Rhesus Monkeys.

(A) The peripheral end of the divided cervical sympathetic was grafted to :—

(1) The central end of the divided hypoglossal, end to end, or to the side of the hypoglossal, end to side.

(2) The central end of the divided superior laryngeal, end to end, or to the lower border of the superior laryngeal, end to side.
(3) The central end of the divided motor portion of the superior laryngeal, end to end.
(4) The central end of the divided descendens noni, end to end.
(5) The central end of the divided phrenic, end to end.
(6) The anterior primary division of the 5th cervical nerve, end to side.

The animals remained alive from 30 to 226 days after the experiments were done. In all the 13 experiments the ocular signs disappeared except in three animals in which death occurred at an early stage of the experiment. Great improvement of the ocular signs was observed 60 days after the operation, and in 100 to 120 days little difference, if any, could be seen in comparing the two eyes. Perhaps a quicker recovery occurred when the peripheral cervical sympathetic was united to the proximal hypoglossal, the proximal phrenic or to the side of the 5th cervical nerve than when anastomosed to other nerves.

(B) In 15 experiments the peripheral end of the cervical sympathetic was left ungrafted to another nerve. The animals remained alive after the experiments for from 32 to 323 days. With the exception of two cats no change in the ocular signs was noted. In Experiment 2 the ocular signs were apparently cured on the 86th day by Faradism. In Experiment 11 slight exophthalmos was observed on the 172nd day, but the other ocular signs due to division of the sympathetic showed no change.

Remarks.—The whisker hairs did not seem always to droop, or else the drooping was so slight that it was not observed. The disappearance of the drooping of the whisker hairs was the first hint that recovery was taking place. The recovery of the ocular signs was first shown by the advancement of the eyeball so that enophthalmos was no longer present. The improvement in the size of the pupil and its reactions so that it became in all respects comparable to the opposite or normal pupil took a much longer time. The last sign to disappear was the prominence of the membrana nictitans. Even when there was no evidence of other ocular signs a slight indication of the membrana nictitans sometimes remained at the inner canthus.

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THE INFLUENCE OF SECTION OF THE VESTIBULAR NERVE ON THE SINGLE-SHOCK REFLEX FLEXOR RESPONSE.

BY E. G. T. LIDDELL, K. MATTHES, E. OLDBERG AND T. C. RUCH.

(From the Laboratory of Physiology, Oxford.)

In a recent communication, Fulton, Liddell and Rioch described the influence upon the knee-jerk of unilateral destruction of the vestibular nuclei and of the eighth nerve [7]. They found an increased susceptibility to inhibition of the knee-jerk, together with a diminution in the postural reflexes of the same side. The behaviour of a flexor muscle under the same conditions presented itself as an obvious sequel for investigation.

We have examined and now offer an account of a brief series of similar lesions in relation to the reflex responses to single-shock stimuli of a flexor muscle, tibialis anticus.

Method.

Making the lesion.—The animals used were cats. Under deep anæsthesia with pure ether and with full aseptic technique, the occipital ridge was exposed and a trephine opening made just caudal to the ridge and some way lateral. The dura was opened and the subjacent cerebellar tissue gently retracted in a medial direction. Very little retraction exposed the eighth nerve at the bottom of the wound. The nerve was then severed with a small hooked knife. A smart brief hæmorrhage denoted severance of the accompanying artery. After hæmostasis, the wound was closed aseptically. Recovery was uneventful, except for the usual movements of spontaneous forced rolling. These could be so violent that asepsis of the skin-wound was endangered and so it became our custom to proceed with recording after only a few days' delay. During this time there was hypotonia on the side on which the eighth nerve was severed. Our preparations were, therefore, examined the first week after section of the labyrinthine nerve, during the stage of recovery when those symptoms are most in evidence which are ascribed to "irritation" (an unhappily vague term, discussed later in this paper).

In one preparation, the rubrospinal tract was divided by a stab in the floor of the fourth ventricle.

Recording.

Decerebration at mid-collicular level was performed under deep anæsthesia and the customary dissection made for myographic examination, viz., immobilization by nerve or tendon resection of all muscles of the hind limb except the two used for myographic examination, the left and right tibialis anticus, so that the limbs of the operated and unoperated side could, each in turn, be examined myographically by changing the position of the preparation in relation to the myograph. The popliteal nerve on each side was prepared for stimulation by Sherrington's glass-shielded electrode. The stimulating apparatus consisted of a students' coil (coreless) fed by a 2-v. accumulator. The primary coil was in series with a resistance box (P.O.) and the break key of a Lucas pendulum. The secondary coil was set at zero. The myograph was a frictionless optical model. The initial tension on the tendon was 60 grm. and observation was made on the strength of stimulus needed to elicit a barely visible reflex twitch of 3-grm. active tension and one of 170 grm. tension, the muscle shortening 1 mm. for 200 grm.

Results.

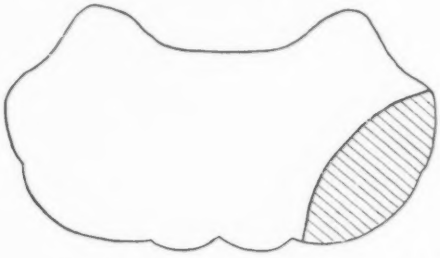
We found a difference between the reflex excitabilities of the motor centres on the two sides. On the side opposite the lesion, that is, on the side which, as many observers have noted, is clinically hypertonic, we

Days after section of 8th nerve	Ohms in primary for a 170-grm. break-shock reflex. (Average of decerebrate with both vestibular nerves intact, from another series of experiments, 40; values below 40 commonest)		Ohms in primary for 3-grm. break-shock reflex. (Average with both vestibular nerves intact 330; values below 250 commonest)	
	Same side as section	Opposite side	Same side	Opposite side
6	135	310	245	1,080
Same day	55	100	240	770
1 (Partial section; ataxy without forced rolling)	105	250	220	360
1	—	190 90	—	370 280
2	5	5	160	350
1 (Both sides operated)	30-40		310-325	
1 (Almost complete)	870	40	1,580	500

found an increased excitability of the flexor's reflex centre. On the side on which the vestibular nerve was cut, that is, on the hypotonic side, the threshold of stimulus needed was as a rule rather lower than normal but was less low than on the unoperated side.

Our results can be set out in a table (see above).

The first five experiments are in accord with fairly close correspondence in values for the 3-grm. twitch. It is interesting to note the difference in the last experiment, in which an unidentified portion of the nerve remained intact. In another animal in which the rubrospinal and neighbouring tracts had been divided seventeen days previously by sectioning a wedged-shaped area in the pons just headward of the emergence of eighth nerve (see figure) the values were:—



	Ohms for 170-grm. reflex twitch		For 3-grm. twitch	
	Same side as section	Opposite	Same side	Opposite
	17	120	310	515
After complete section of the cord	75	470	190	590

This preparation, therefore, reacted in the same way as the majority of vestibular preparations.

Discussion.

The importance of the contribution from the vestibular nuclei for maintaining decerebrate rigidity is well established. If these nuclei or the tracts carrying their impulses are injured or ablated, rigidity very largely disappears, that is, hypertonus in extensor muscles is replaced by almost complete flaccidity in all muscles and the reactions of the preparations become "spinal" [7]. (The knee-jerk is then more easily inhibited by external stimuli [2] and "pale" rapid muscle is in abeyance [4].) These effects on extensors are ipselateral and unilateral. *A priori* some change in the antagonists of the extensors might be expected and that on the same side. Our series, however, show less

increase in excitability of the ipselateral than of the contralateral flexor. The contralateral increase may be due to a change in the intensity or extensity ("fringe") [5] of the subliminal excitation which is streaming down the long paths from the undamaged vestibular apparatus. On the other hand, there may be a decrease in inhibition such as occurs when the spinal cord or certain tracts within it are severed [13, 14]. This latter view is supported by the evidence presented in the accompanying paper that section of the lateral, medial, ventral reticulospinal tracts and of the vestibulospinal tract in the spinal cord releases the flexor centre from inhibition and makes it more easily excited [9]. But we have, in fact, no accurate evidence of the precise method by which the hyperexcitability on the contralateral side is brought to pass. That there is normally some sort of balance of function between the two labyrinths has long been believed. The crossed vestibular root which crosses the midline to the medial and lateral vestibular nuclei of the opposite side is probably an important path in correlating the functional activity of one labyrinth with that of the other. By its agency, one labyrinth can interact with the other either to increase excitability or decrease inhibition, or to effect both these results. Of descending tracts which pass down the cord on the side opposite their origin, there are the crossed vestibulospinal tract which arises from the descending vestibular nucleus of the opposite side and fibres in the medial longitudinal fasciculus from the medial vestibular nucleus of the opposite side. Part of the medial reticulospinal tract originates on the crossed side. The ventral reticulospinal tract has a crossed origin. The lateral reticulospinal tract has a crossed origin, but no close association with vestibular nuclei [8, 11, 12]. Therefore there exists at the level of both the first and second order neurones a possible basis for the effect we have described.

That extensor muscles of the side opposite the vestibular lesion show increased excitability is well known and evident enough before decerebration. We now record an increased excitability in the corresponding flexor centre. On the homolateral side, however, extensors are depressed and flexors but little affected. We conclude, therefore, that section of the vestibular nerve on one side changes the pattern of reflex response from that which obtains in the customary "intercollicular" preparation. Thus, although our wording is, of set purpose, different, we support the the conclusion reached by Camis, "labyrinthectomy alters the normal reciprocal activity of, e.g., flexor and extensor muscles of the leg" [3]. A conclusion in such words unjustifiably suggests a modification of the

principle of reciprocal innervation, as Creed has pointed out, for the results may be due, in part, to the use of a "mixed" afferent nerve and cannot be ascribed entirely to labyrinthectomy. Our results may also be due, in part, to the same cause, since the popliteal nerve, so far as tibialis anticus is concerned, contains inhibitory as well as excitatory fibres [6]. Rather should it be said that labyrinthectomy alters the balance of the reflex background upon which the mixed afferent is brought to play. So the appearance of the resulting action is altered, although each component of the "mixed" nerve presumably continues to act reciprocally (though oppositely) on the flexor and extensor motor neurone. It must further be remembered that the non-auditory part of the eighth nerve itself is probably a "mixed afferent," since there is considerable evidence that the labyrinth is composed of a number of distinct but correlated functional entities [10]. By section of the labyrinthine nerve we have therefore deprived a reflex mechanism of a stream of impulses of varying import and then have brought to bear from the outside stimulation by a "mixed" afferent nerve. The increased excitability of the contralateral flexor which we find to be the consequence points either to a decreased inhibition or an increased excitation for its probable cause, or both.

In regard to the first possibility it is known that section or partial section of the spinal cord brings about lowering of the flexor threshold, which strongly suggests "release" from the inhibition of higher centres [13, 14]. On the other hand, the clinical state of the animals in the present experiments, with spontaneous rolling movements and contralateral hypertonia, tempts us to suggest that the origin of this increased excitability is the labyrinthine mechanism on the uninjured side, now no longer "balanced" against or inhibited by its fellow of the other side. In other words, our experimental procedure has not removed a direct inhibition but has upset a pre-existing balance of inhibition and produced excitation. If such an hypothesis be adopted, it need not negative the possibility that release of flexor centres by spinal section implies the cessation of higher *inhibitory* influence, for both inhibition and excitation from medullary and higher centres operate by long paths upon the lower spinal centres and the spinal paths subserving each process need not lie in the same anatomical region of the cord, any more than their centres of origin need be contiguous in the medulla. The belief that the lowered threshold of flexors is brought about by at least two processes receives support from study of the figures after complete spinal section in ordinary decerebrate preparations given in the accom-

panying paper [9]. In them, the threshold of the flexor centre is considerably lower than that resulting from section of the contralateral labyrinthine nerve, that is to say, the maximum degree of release is not achieved only by section of the labyrinthine nerve, but further release is possible by section of some spinal tract such as the reticulo-spinal. In our present brief series of experiments, it has not been possible to test this hypothesis by a search for further lowering of threshold from such a cause.

It is possible that injury of the vestibular nucleus, as opposed to section of the eighth nerve, might have had for the flexor a different result, as was noted for the extensor by Fulton, Liddell and Rioch. Spiegel [15] has observed that some factor or locus is concerned in the maintenance of decerebrate rigidity in addition to the vestibular nuclei. He has suggested the reticular substance of the medulla. In our own results with the flexor, the increase from vestibular section of contralateral excitability falls short of the increase produced by spinal section. It seems likely therefore, that for the flexor as for the extensor there is some factor in addition to the vestibular apparatus for " release " of the former.

The relation between this hyperexcitability of contralateral flexors and extensors is probably a close one. It is well known that some days after total unilateral labyrinthectomy, the forced movements cease to be spontaneous but can be elicited by rotation of the animal's snout. It remains, therefore, to inquire whether the excitability of the spinal centres, as revealed by our experiments, decreases *pari passu* with the reduction of forced movements. Such an investigation might also throw light on the cause of origin of these movements, whether due to permanent functional deprivation or to transient operative " irritation." The processes underlying the stage " irritation," to which have been ascribed the earlier signs such as forced rolling, are difficult to define. Nerve injury currents cannot play any part since they subside in a few minutes or hours and do not endure for days [1]. Inflammation due to sepsis is not there. Œdema only seems more possible. But in our opinion the early stage may well be due to acute lack of compensation following the functional removal of one labyrinth. The later stage, ensuing after a week or two, which has been called the " deficiency " stage, is due certainly to deficiency, combined probably with some degree of compensation, and following disuse or inhibition of previously active nerve-paths, or it may be due on the other hand to the activation of previously less active paths.

SUMMARY.

In cats the hypertonia which occurs in the opposite side during the first week or two after experimental severance of the eighth cranial nerve is accompanied by an increase in excitability of the spinal centres of tibialis anticus, a flexor muscle. There is a slight lowering of threshold also in the ipselateral flexor centre. It is pointed out in discussion that this increased excitability, with its well-known clinical accompaniment of spontaneous rolling movements and of hypertonia, may be due directly to deprivation of the opposite labyrinth,and though less in degree, is comparable to the lower reflex threshold of flexor centres brought about by spinal section. But tentatively we hold to the hypothesis that it results from overaction of the intact ipselateral labyrinth, now no longer " balanced " or inhibited by its fellow labyrinth.

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REFLEX RELEASE OF FLEXOR MUSCLES BY SPINAL SECTION.

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INTRODUCTION.

WHEN the spinal cord of a decerebrate preparation is transected at a low thoracic level, the flexor reflex undergoes immediate enhancement [9, 10]. The extensors, on the other hand, are depressed by spinal section [9]. For example, the knee-jerk becomes more susceptible to inhibition [1] and the stretch reflex disappears. This effect on the extensors has been traced to the vestibulo-spinal tract as the main agent, though there is a possibility that the reticulo-spinal tract plays an important subsidiary role [2, 11].

The spinal tracts whose section is responsible for release of the flexor centre remained for investigation and we now describe experiments performed with that object in view.

METHOD.

The animals used were cats, to the number of twenty. The experiments were acute, that is to say, the preparations were observed within a few minutes or hours of the spinal lesion. The animals were decerebrated under profound C.E. anæsthesia, the cord exposed by laminectomy at a low thoracic level and the usual immobilization of the hind limbs obtained by tendon or nerve resection for all muscles, except tibialis anticus in each leg. The ipselateral popliteal nerve was prepared as an afferent for stimulation by Sherrington shielded electrodes. Some hours later, when the effects of the anæsthetic had worn off, the preparation was rigidly fixed by drills through the tibia and mounted under a shadow myograph of torsion-strip frictionless type. To elicit a single-shock flexor reflex the ipselateral popliteal nerve was stimulated by a students' coil (coreless) with the secondary set at zero. A 2-v. accumulator fed the primary through a resistance box (P.O.), which was used to regulate the strength of stimulation. A Lucas pendulum broke the primary circuit. Two strengths of stimulation were sought, one

necessary to elicit a barely perceptible twitch (3 grm.), the other a twitch of 170 grm. active tension. The initial tension was 60 grm. In some earlier experiments, the strength of stimulus required was obtained by moving the secondary coil and not by altering the resistance in the primary circuit.

The dura mater was then opened and a selected part of the cord severed with a Saunders' discission needle at a low thoracic level. It was possible to place the lesion in the desired area. Its position was confirmed by subsequent examination after twenty-four hours' fixation in formalin. On occasion, the dura was opened before myographic examination, and immediately after laminectomy. At the same time a lesion of the cord was made. This alternative but less frequent procedure gave results in correspondence with the usual procedure. The lesion was usually made so as to be unilateral. By moving the preparation under the myograph, it was possible to examine each limb in succession. Before the infliction of any lesion, the difference between the two sides was very small. After a unilateral lesion, the change was almost entirely in the limb of the same side.

It has long been established that section of the cord in the lower thoracic region enhances the decerebrate rigidity of the forelimbs. Although we have made no specific observations on the tract concerned, the enhancement follows injury of ipselateral tracts. Immediately or within five seconds of infliction of the lesion, the ipselateral forelimb becomes rigidly extended forwards. Half a minute later, the contralateral forelimb follows suit.

In most preparations, making the lesion is followed by a short-lasting reaction and within two minutes spontaneous muscular movements cease and acceleration of the heart-rate comes to an end. In less favourable preparations, impairment of the circulation and respiration continues. It is well known that impairment of this kind alters the reflex background.

Results.

Sherrington first described enhancement of the flexor reflex by (total) spinal section [9] and he and Sowton found that the enhancement is considerable, as a rule [10]. In non-rigid preparations, however, the change was often slight and sometimes lacking. We, too, found that enhancement of the reflex might reach, in most preparations, a very high value, e.g., ten times as measured by the ohmage in the primary circuit. These high values were obtained only in lesion of the cord of the same side. In none of our experiments did a lesion of the opposite

side of the cord ever effect more than a one-tenth increase in value, unless the lesion transgressed to the homolateral side. Sometimes a lesion of the opposite side produced a small *decrease* in excitability. The homolateral side has by far the more important influence in releasing the flexor centre. In only two preparations of our series did partial lesion fail to produce any change. But in these, complete section was also without effect. The release after the lesion is immediate and maintained for at least two hours, our longest observation. In some preparations the release became a little more marked during this time.

We found that when observations were taken in rapid succession, e.g., at two-second intervals, there was a very definite facilitation. A single-shock stimulus, for instance, when first applied might evoke a contraction of 4 mm., but if reapplied within two to three seconds the contraction rose to 5 mm., and did not, as a general rule, increase thereafter. It therefore became our custom not to record the first, but only subsequent responses.

This facilitation in the decerebrate preparation led us to investigate the state after tetanic stimulation. Facilitation was then considerable. Our method was as follows: A strength of stimulus was selected which gave, as a single shock, a contraction value of 170 grm. This was then applied as a tetanic stimulus (35 p.s.) for five seconds. At subsequent intervals the stimulus was then given as a single stimulus. In a typical response the tension was more than three times the original at an interval of one-minute after the tetanic stimulation, more than double at three minutes, and so continued for six minutes more. After twenty minutes from the onset, the threshold for 170-grm. twitch was still one-quarter of its original value. It was interesting to find that by cord section one and a quarter hours previously, the effect disappeared almost entirely, being only one-fifth more after thirty seconds, and normal after sixty seconds. The abolition of facilitation of this type therefore appears to depend on the severance of the paths from higher centres, and on the resulting deficiency of excitation reverberating from them.

In analysing the release resulting from partial spinal section, our experiments fall into two groups. In the first group, which is much the larger, one partial lesion, if restricted, never does more than half the threshold. In it are found the preparations in good physical condition circulation and respiration of which suffer little, if any, permanent impairment from the partial lesion. We describe the second group later in this paper. It comprises preparations in less good condition in which the threshold is lowered ten or twelve-fold by small spinal lesions.

Group I.—Our lesions were not always placed in definite areas, nor made in the same order. It was convenient for the purpose of assessing

Ex. No.	Threshold for 170 grm. single shock reflex: Decerebrate before any ipsilateral lesion	Threshold for 170 grm. single shock reflex: After complete spinal section	Rise (ohms)	Percentage, due to each area, of total change after complete spinal section. The heavy underline denotes that those areas were transected by the same lesion. The **index number** at the end of the heavy line gives the order in which the lesions were made. "Post."	"Post. Lat."	"Lat."	"Ant. Lat."	"Opp. Ant. Horn."	"Ant."
1	65	85	20	100	100	0			
2	40	280	240	58	58	0	0	37	37
3	5	370	365	16	16		2	2	2
					82′	82′			
4	5	159	154		76	76			
				0	0	0	0	0	26
5′	140	400	260		40	40	60	60	60′
6	0	370	370	100	100	0	0	0	0″
7	30	820	790	0		0			
8	5	140	135	0	0	0	0	75	75′
									25′
9	10	360	350	0		0		45	45
					55				55
10*	12·6 cm.	24·6 cm.	12 cm.	75	75 (approx.)				
Average rise in threshold for injury in each area, but the figure must be offset against the per cent. frequency of zero change				38 44	54 11	20 66	17 71	31 43	39 29

(′) Values obtained by semi- or total section at conclusion of experiment.

(″) Semi-section of opposite side during morning.

(s) Superficial lesion.

(*) An early experiment when strength of shock was graduated by moving the secondary coil.

results to map the cord into areas as shown in fig. 1. Since a lesion was often made to pass through more than one area, it is possible that an inactive area bordering on an active area might acquire an undeserved reputation. This has been counteracted by showing the number of times on which lesions of the areas gave no change. Thus it appears that any lesion on the ipselateral side can on occasion lower the reflex threshold. There are, however, two regions of special susceptibility which also are constant in showing susceptibility and seldom show no change at all. These regions are the postero-lateral and the anterior.

In the above experiments, there was no tetanizing stimulation of the preparation for the establishment of facilitation (p. 241). Facilitation experiments have been discarded for purposes of this assessment. The changes recorded were due only to the spinal lesion.

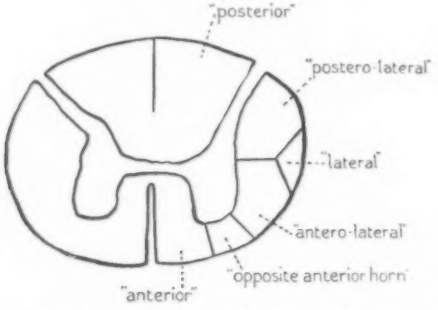

FIG. 1.—To show diagrammatically the regions described in the text.

Postero-lateral region.—In considering the anatomical tract in this region whose section might bring about release, it is possible to eliminate the pyramidal tract, which although present in the cat in the lower dorsal region, cannot be involved since it has been sectioned already by the decerebration. Also, in most of our preparations, it was possible definitely to exclude the rubrospinal tract since the level of decerebration was often at or caudal to the intercollicular level, so that the greater part of the red nucleus was already ablated, and any part which might remain would suffer considerable impairment from œdema and exposure. The tract with which we are concerned is not near the surface of the cord since superficial lesions do not establish any striking release. But an important descending tract which is located deep in the postero-lateral region is the lateral reticulo-spinal (fig. 2). By the degeneration experiments of Papez [7] and Gray [5], it is seen to be a considerable

link between the reticular formation of the medullary region and the lower spinal centres [8]. Since we find, by physiological experiment, that the area through which the tract runs is one whose section gives release to flexor centres from higher control, we conclude that the lateral reticulo-spinal tract is probably itself the path by which impulses descend in the decerebrate preparation to check flexor activity. The uncinate fasciculus of Russell, which occupies the same region as the lateral reticulo-spinal tract, does not descend lower than the level of the second cervical nerve and can therefore be disregarded for present purposes.

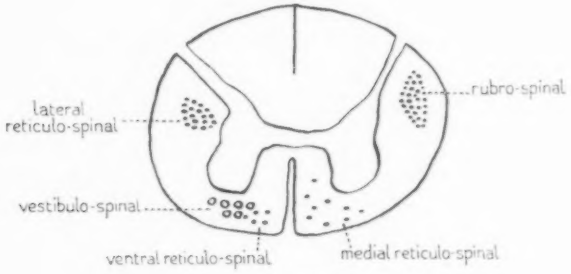

FIG. 2.

Anterior region.—In the production of spinal shock in extensor muscles and their increased susceptibility to inhibition after spinal section, Fulton, Liddell and Rioch [4] established the importance of the vestibulo-spinal tract, although that was probably not the only tract, because section of the vestibular tract itself was less effective than section of the anterior quadrant of the cord [cf. 11]. In view of their results, it might be expected *a priori* that the same tracts would be concerned in the release of the flexor centres from higher control, and we have found, as pointed out above, that the anterior region of the cord is susceptible as well. In an accompanying paper, where experiments are described in which the vestibular nerve was sectioned intracranially, evidence is presented that those tracts have this function also for flexors [6]. In addition, the ventral and medial reticulo-spinal tracts (see fig. 2) are in all probability concerned, though their relative importance has not been estimated. The vestibulo-spinal tract extends rather more laterally than the ventral reticulo-spinal and its coming into our anterior area would account for the constant moderate release achieved by section in that area.

As mentioned above, we have not found any considerable or constant release from sections of the cord on the opposite side. Although there are crossed reticulo-spinal tracts and also slender crossed vestibulo-spinal tracts, their decussations are well above the level of the spinal cord and therefore above the level of our lesions.

Group II.—In assessing the second group of results, in which there were falls of threshold as much as ten-fold, impairment of the preparations, circulation and respiration seemed to be an important accompaniment. The average of this series for the posterior funiculi is a four-fold increase, for the other funiculi six to seven-fold without clear differentiation. Certain preparations, therefore, are so unstable that any considerable division of any path in the postero-lateral and anterior regions is likely to give an apparent, even if not a direct, release. But such preparations are only obtained from animals in imperfect health, with an impaired vascular system, and taken from an unselected laboratory stock. The release in such cases is the maximum possible for that preparation. These unstable preparations giving maximum release are therefore less useful than the more resistant preparations for purposes of relative assessment.

Summary.

The enhancement of the flexor reflex in decerebrate preparations resulting from total spinal section is due, in fact, to transection of two susceptible ipselateral regions, the postero-lateral and the anterior. The tract in the postero-lateral region is probably the lateral reticulo-spinal tract, and in the anterior region the vestibulo-spinal and ventral and medial reticulo-spinal tracts are probably chiefly concerned.

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SPASTIC PSEUDOSCLEROSIS (CORTICO-PALLIDO-SPINAL DEGENERATION).[1]

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I.—Introduction.

The clinician and the pathologist are occasionally confronted with morbid processes which do not conform to any of the recognized clinical syndromes. I have recently seen two such cases. The disease occurred in two adults; it ran a rapid course; and it was characterized clinically by mental symptoms, pyramidal and extrapyramidal signs, and muscular atrophies. Histopathologically, there were changes in the nervous system corresponding to these clinical findings. These two cases at one time were considered with four others as unusual instances of amyotrophic lateral sclerosis with mental symptoms. The extrapyramidal symptoms and the histopathological changes found in the pallidum make it doubtful if they belong to this group.

II.—Report of Cases.

Case 1.—J. R., male, aged 32, was admitted to the hospital on May 30, 1930. In December, 1927, he noticed the onset of weakness and unsteadiness of the left lower extremity which remained unchanged until April, 1929, when, following a sore throat, he developed difficulty in speech and weakness of the upper extremities. Examination in November, 1929, showed gluteal atrophy, exaggeration of all deep reflexes, more on the left, a left Babinski sign, left facial weakness, deviation of the tongue to the left, marked dysarthria, dysmetria of the left upper extremity, spastic ataxia of the left leg, and a slowness and slurring of speech. Multiple sclerosis or a degenerative disease of the nervous system were considered as diagnostic possibilities. There was no history of influenza or encephalitis. The family and past history were unimportant.

Neurological examination in May, 1930, revealed a bedridden young adult with rigidity, drooling, spasmodic laughing and crying, and unsteadiness of the upper limbs. The speech was dysarthric, explosive, scanning, and at times

[1] From the Neuropathological Laboratory, Montefiore Hospital, New York.

monotonous. The interosseous muscles were atrophied and there were generalized fibrillary twitchings, massive in character, of the arms, forearms, hands, legs, shoulders, and girdle muscles. There was increased tonus in all four limbs, and cog-wheel rigidity in the upper limbs. The left foot had a striatal attitude. Power was diminished in all extremities, more on the right side. There was generalized bilateral increase of the reflexes with positive Babinski sign and absent abdominal reflexes. The fundi were normal. The face was oily. The right corner of the mouth drooped. Emotional movements were good. The tongue deviated to the left. The patient was deteriorated, apathetic, inco-operative, and disoriented. His memory was poor for recent and remote events. He usually responded to simple commands, but more complicated ones elicited no response whatsoever.

His other organs were normal. X-rays of the skull showed a faint streak of calcification above and to the right of the pineal gland. The possibility of a neoplasm was considered. All other laboratory data were negative.

The patient gradually developed difficulty in swallowing and breathing. On November 7, 1930, he developed fever and cyanosis, and died of aspiration pneumonia the following day.

Pathological findings: Permission for the removal of the brain and spinal cord only was obtained.

Brain.—The convolutions from the frontal to the post-central regions were atrophic and the fissures were widely separated. The blood-vessels were markedly congested. The cortical gray matter appeared thin. The white matter of the right corona radiata, in sections through the caudate and putamen, was shrunken.

Spinal cord.—The cord appeared anæmic. On transverse section there was translucency of the crossed pyramidal tracts. The gray matter was slightly hæmorrhagic.

The brain and spinal cord were preserved in 10 per cent. formaldehyde. Frozen and celloidin sections from the entire nervous system were stained by the myelin sheath stain (Weil modification), Mallory's phosphotungstic and hæmatoxylin, hæmatoxylin-eosin, cresyl violet, Sudan IV, Cajal's gold sublimate (Globus modification), Bielschowsky's, Del Rio-Hortega's (Penfield's modification) and Anderson's Victoria blue methods.

Microscopical Examination.

Cerebral hemispheres, frontal lobes.—The pia-arachnoid was thickened in places and there was proliferation of the arachnoidal cells. The meningeal vessels showed moderate atherosclerotic changes. The arrangement of the cortical architectural layers was fairly well preserved. The ganglion cells of the third, fifth and sixth layers were diminished in number. Some cells were shrunken, had deeply stained nuclei, reticular protoplasm and corkscrew processes; others were swollen, the nuclei were at the periphery of the nerve-cells, and the tigroid substance had disappeared completely. The cells of the fifth layer were more involved than those in the other layers. The nerve-cells

in this area were completely disintegrated and showed marked chromatolytic changes. With the Sudan IV stain lipoid granules were found in the ganglion cells. Definite foci of destruction were present. There was an increase in the smaller vessels of the cortex, a few showed intimal proliferation, and some were completely occluded. There was an enormous proliferation of microglia cells in the third, fifth and sixth cortical layers; some were hypertrophied (fig. 1). The protoplasmatic astrocytes were also increased in number. The white matter, particularly on the right side, stained poorly, but did not show any evidence of breaking down of myelin. The Cajal gold sublimate stain of the white matter disclosed numerous enlarged astrocytes.

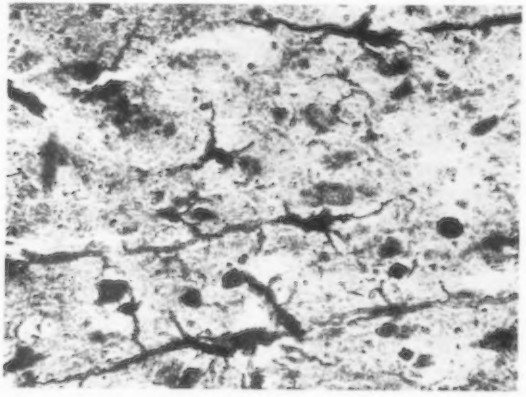

FIG. 1.—Increased and hypertrophied microglia cells in the cortex. Silver carbonate stain (Penfield's modification). × 400.

Precentral gyrus.—The same changes were observed as in the frontal gyri, except that the normal architectural arrangement of the cortical laminæ was lost. The giant pyramidal cells of Betz were fewer in number, were disintegrated, and had ill-defined nuclear bodies and very little Nissl substance. There was also neuronophagia. The capillaries, microglia and protoplasmatic astrocytes were increased in number. There were no giant astrocytes. The white matter was filled with proliferated and occluded small vessels, some of which showed evidence of beginning calcification.

Hippocampus.—There was falling out of ganglion cells with the changes seen in the acute and chronic stages of degenerative diseases. Occasional neuronophagia was also observed here. The microglia and protoplasmatic astrocytes were increased in number.

Sections from the parietal, temporal and occipital regions, except for occasional poorly-stained ganglion cells, showed nothing of note.

Basal ganglia.—The *caudate nuclei* were normal. *Putamen*: The small and

FIG. 2.—Section through the neostriatum and rostral end of the globus pallidus showing poorly stained white pallidal fibres, more so on the right. Myelin sheath stain (Weil modification).

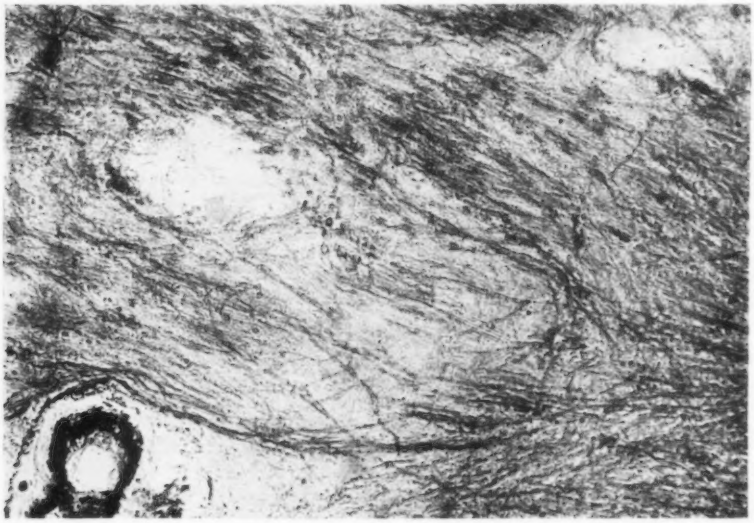

FIG. 3.—Disintegration of the white fibres from the globus pallidus. Myelin sheath stain (Weil modification). × 480.

large ganglion cells were fewer in number, some showed loss of Nissl substance and eccentrically placed nuclei, and others were completely disintegrated. Neuronophagia was rarely observed. The nerve cells of the amygdaloid nuclei appeared normal. *Globus pallidus*: The white fibres of the globus pallidus took the myelin sheath stain poorly (fig. 2). Under higher magnification some of the pallidal fibres, especially those on the right, were demyelinated. Some of the myelin sheaths were completely broken down and others were swollen (fig. 3). A number of the vessels were markedly sclerosed and calcified (fig. 4*a*). About the calcified vessels the pallidal cells were decreased in number, shrunken,

FIG. 4*a*.

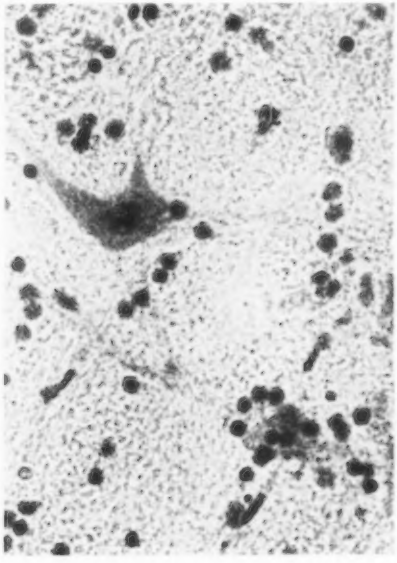

FIG. 4*b*.

FIG. 4*a*.—Section from the globus pallidus showing calcification of the blood-vessels and decrease in the number of ganglion cells. Cresyl violet stain. × 120.

FIG. 4*b*.—Two ganglion cells from the globus pallidus; one showing satellitosis, and the other poor chromatin substance. Cresyl violet stain. × 700.

had a homogeneous appearance, showed poor chromatin substance and some were completely destroyed. Some of the ganglion cells showed vacuolation. Occasional neuronophagia was also observed (fig. 4*b*). In places there was a slight increase in the number of protoplasmatic astrocytes and microglia. A few amyloid bodies were seen. Most of these changes were found in the rostral and middle portions of the globus pallidus.

Corpus Luysii.—The same changes were found here as in the globus

pallidus, but not quite so marked. There were no calcified vessels and the nerve-cells were somewhat better preserved. The superior part of the right internal capsule contained a few vessels with round-cell infiltration in the perivascular spaces.

The paraventricular nuclei.—The nerve-cells showed marked destruction, otherwise the changes were about the same as those observed in the cortex and globus pallidus.

The thalamus, substantia innominata of Reichert, red nucleus and substantia nigra were normal.

Sections in the region of the posterior commissure and pons.—The pyramids were poorly stained. With higher power some of the myelin sheaths of the

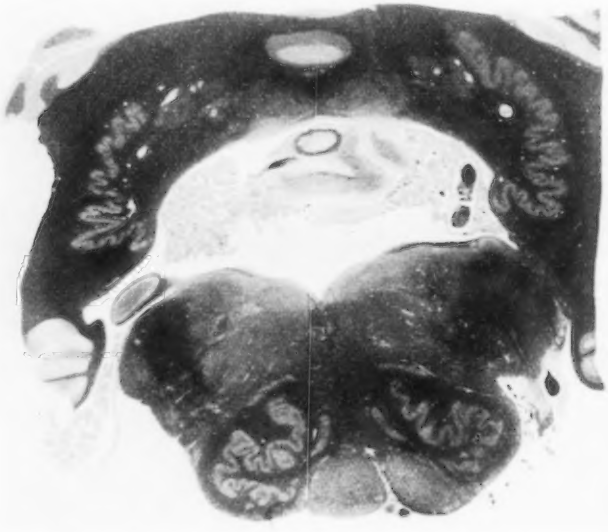

FIG. 5.—Lacunar state in the region of the dentate, emboliform and globose nuclei. Demyelination of the pyramids in the medulla oblongata. Myelin sheath stain (Weil modification).

pyramidal fibres appeared disintegrated. Sections in the region of the colliculi, cerebellum and pons showed marked thickening and fibrosis of the pia-arachnoid. Psammoma bodies were found within this fibrosed tissue. The white matter of the cerebellum did not take the myelin sheath stain well and with higher magnification occasional fibre disintegration could be observed. The architectural layers of the cerebellum were well preserved, except for poor staining of the Nissl substance in the Purkinje cells. The dentate, emboliform and globose nuclei presented a lacunar appearance (fig. 5). A few of the nerve-cells of the dentate nucleus showed changes similar to those found in the

cortex. The pyramids of the medulla oblongata were demyelinated (fig. 5). Some of the myelin sheaths were broken down and others showed signs of swelling. The cells of the nucleus ambiguus were fewer in number, showed poor Nissl substance, eccentric nuclei and occasional neuronophagia. The nuclei of the other cranial nerves presented very slight changes. The nerve-cells of the superior and inferior olives were intact.

Spinal cord.—Sections at various levels showed demyelination of both crossed and the right anterior pyramidal tracts (fig. 6). With higher magnification the changes previously described in the pyramids were found, and in addition a honeycomb appearance and a more advanced disintegration of the myelin. In the Bielschowsky preparation the axis-cylinders were completely broken

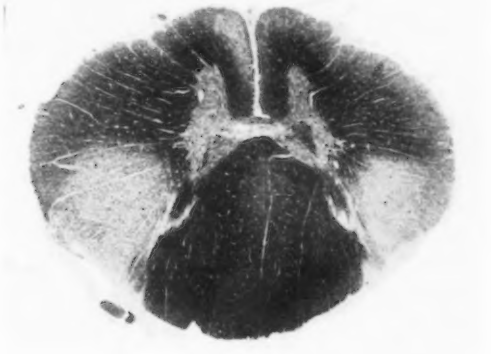

FIG. 6.—Transverse section of the spinal cord in the mid-thoracic region, showing demyelination of the lateral pyramidal tract and the right anterior pyramidal tract. Myelin sheath stain (Weil modification).

down and had a corkscrew appearance. The demyelinated areas were replaced by densely packed glia fibres. The anterior horn cells were decreased in number; some were shrunken, amorphous, deeply stained and devoid of Nissl substance. Homogenization and collection of tigroid substance at the periphery, with eccentrically placed nuclei, were also observed. There was a slight increase in the glia cells within the gray matter. These changes were observed throughout the spinal cord, except in the sacral region.

Comments.—The diagnosis rested at first between multiple sclerosis, the lenticular syndrome (Wilson's disease or pseudo-sclerosis) and amyotrophic lateral sclerosis with mental symptoms. The histopathological findings were: atrophy of the cerebral convolutions from the frontal to the parietal regions; scantiness and destruction of the ganglion cells in

the third, fifth and sixth layers; areas of devastations; proliferation of the vessels; increase in the microglia and protoplasmatic astrocytes of the cortical gray matter and in the astrocytes of the white matter; marked destruction of the giant pyramidal cells of Betz; demyelination of the pallidal fibres; calcification of the pallidal vessels; destruction of the nerve cells of the pallidum, corpus Luysii and paraventricular nuclei; degeneration of the pyramidal tracts and degenerative changes in the anterior horn cells. There was no evidence of encephalitis. The few inflammatory cells found in the perivascular spaces of the internal capsule could have no bearing on this disease process. There were no giant glia cells as observed in Alzheimer's disease or pseudo-sclerosis. The histopathological changes resembled the findings in the latter two diseases, except for the absence of plaques and giant glia cells. The pathological findings in the spinal cord were those of amyotrophic lateral sclerosis.

Case 2: E. G., female, aged 50, was admitted to the hospital on July 19, 1930, in a semi-stuporous condition, with a temperature of 104° F., and died the next day. In January, 1929, she complained of headache and pain in both shoulders radiating to the lumbar region. At the beginning the pain was mild, later it became severe. In May, 1929, she had difficulty in walking and spasticity of the lower extremities. She also complained of polydipsia and polyuria. Two months before admission to this hospital she became drowsy and mentally confused. At two other institutions the diagnosis first of multiple sclerosis and later of diffuse degenerative disease with mental symptoms was made.

Neurological examination was unsatisfactory because of the mental stupor. She presented a coarse and greasy skin, a tendency to bilateral ptosis, right facial paralysis, spastic paresis of all four extremities, generalized increase of the deep reflexes, bilateral Babinski sign and absent abdominal reflexes, dysmetria, Parkinsonian facies with rigidity of the upper extremities, a tendency to the accoucheur position of the hands and catatonia. Mentally, the patient was confused, co-operated very poorly, showed psychomotor retardation and was emotionally unstable.

Except for a slight secondary anæmia and a trace of albumin in the urine, all other laboratory findings were negative.

Pathological findings: All the organs, except the nervous system, showed a moderate generalized arteriosclerosis. The liver was normal.

Brain.—There was slight atrophy of the convolutions, more on the right, extending from the frontal to the post-central gyri. The fissures in these areas were widely separated and the vessels were congested.

Spinal cord.—The dura was slightly thickened and its inner surface was studded with numerous calcareous bodies. There was a translucency of the

right lateral pyramidal tract in the cervical, mid and lower thoracic regions. Frozen and celloidin sections of the entire nervous system were stained with the same methods as in Case 1.

Microscopical Examination.

Cerebral hemispheres.—Sections of the frontal convolutions showed normal meninges with moderately atherosclerotic vessels. There were no disturbances in the arrangement of the architectural layers of the cortex. The ganglion cells of the fifth and sixth layers were diminished in number. They stained very poorly, were swollen and totally devoid of Nissl substance (fig. 7)

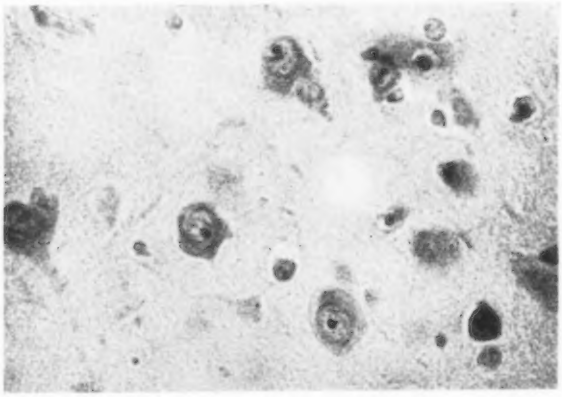

FIG. 7.—Swelling of the ganglion cells from the frontal convolution, eccentric nuclei and poor Nissl substance. Cresyl violet stain. × 700.

The nuclei of most of the ganglion cells of these layers were likewise swollen and eccentric and contained little chromatin. Throughout the fifth and sixth laminæ there was hardly a normal cell. A few of the ganglion cells of the third layer showed similar changes. With the Sudan IV stain lipoid granules were found in the nerve-cells. The glia cells were slightly increased in the third, fifth and sixth layers, and consisted primarily of protoplasmatic astrocytes. Contrary to the findings in Case 1 there was no increase in microglia here. The white matter appeared normal. The larger vessels showed moderate atherosclerotic changes. The smaller capillaries were increased in number as in Case 1 (fig. 8).

Precentral convolutions.—There was a falling out of the ganglion cells in practically all the layers, most noticeable in the fifth and sixth laminæ. The architectural layers were not as well preserved as in the frontal gyri. The giant pyramidal cells of Betz were fewer in number and showed chromatolytic

changes. The more minute histological changes in the ganglion cells were the same as in the frontal region.

Parietal and temporal areas.—Except for marked disarrangement in the cortical layers these showed the same changes as in the previous sections. The gray and white matter of the temporal lobes were studded with numerous lacunæ. The white fibres did not take the myelin sheath stain as well as in the previous sections, although there was no breaking down of myelin. The architectural layers in the middle temporal lobes could barely be made out, and the falling out of ganglion cells and chromatolytic changes were predominant in the third layer, instead of the fifth and sixth as in the other regions. The hippocampus was loaded with numerous corpora amylacea, poorly stained

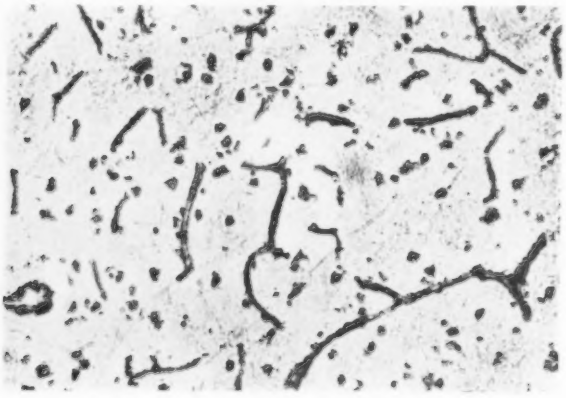

FIG. 8.—New vessel formation in the cortex. Silver carbonate stain. × 200.

ganglion cells, and a few calcified vessels. In the occipital lobes very slight changes were observed.

Basal ganglia.—With the myelin sheath stain the right globus pallidus had a lacunar appearance, and the white fibres stained poorly (fig. 9). Some of these fibres were completely demyelinated. The ganglion cells in the neostriatum, thalamic and paraventricular nuclei, except for an occasional poorly stained cell, were well preserved. In the globus pallidus, however, both the ganglion and the glia cells were diminished in number. The pallidal cells showed acute and chronic changes as swelling, lack of chromatin, homogeneous appearance, and occasional shrinkage and pyknosis. The nuclei were swollen, poor in chromatin material and eccentrically placed. Throughout the pallidum, especially in the inner segment of the middle and caudal parts, numerous calcified blood-vessels were found. Most of the changes of the ganglion cells were found in the vicinity of the calcified vessels. There were no amyloid bodies. New vessel formation, as in the cortex, was also observed here. With the

Sudan IV stain fat was observed in the vessels. The cytoplasm of the nerve-cells was replaced by lipoid granules. The protoplasmatic astrocytes were slightly increased in number.

The corpus Luysii, substantia nigra, and red nucleus.—Except for an occasional disintegrated or poorly stained ganglion cell, these structures showed no abnormalities. A few of the nerve-cells in the oculomotor nerve nuclei showed evidence of pigment atrophy.

The *cerebellum* and *pons* showed no changes. Except for occasional loss in Nissl substance and pigmentation, the ganglion cells of the dentate nuclei were normal.

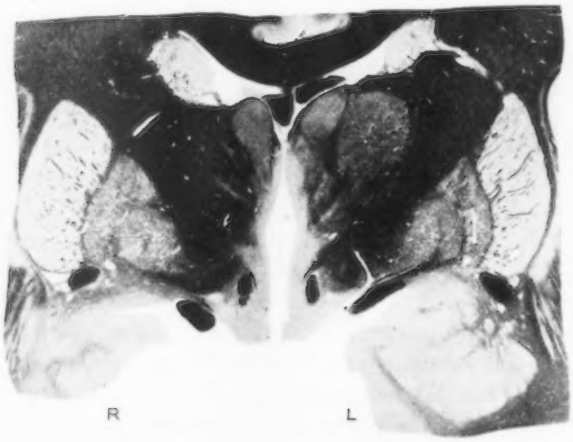

FIG. 9.—Section through the middle third of the globus pallidus showing paleness and a lacunar state of the right inner segments of the pallidum. The white fibres of the globus pallidus on that side did not take the stain well. Myelin sheath stain (Weil modification).

Medulla oblongata.—The pyramids were pale. The nerve-cells of the tenth and twelfth nerve nuclei showed chromatolysis, shrinkage, vacuolation and pigmentary atrophy. The same changes were found in the inferior and accessory olivary nuclei. The nerve-cells of the locus cœruleus contained very little pigment.

Spinal cord.—In sections throughout the cord there was marked demyelination of both crossed pyramidal tracts and to a lesser extent also of the left uncrossed pyramidal tract (fig. 10). A number of the myelin sheaths were completely destroyed and others swollen. Many axis-cylinders were broken down, some had a corkscrew appearance, but a few were fairly well preserved. The glia fibres of the lateral pyramidal tracts were increased in number. The

anterior horn-cells were diminished in number, some were markedly swollen, had a homogeneous appearance, were devoid of Nissl substance, and had swollen and eccentrically placed nuclei. Those of the mesio-ventral group showed poor Nissl substance and atrophy. These changes in the ganglion cells were observed throughout the spinal cord, except in the sacral region, and were most marked in the thoracic region. The vessels were normal, the meninges were not thickened, and there was no evidence of any perivascular infiltration.

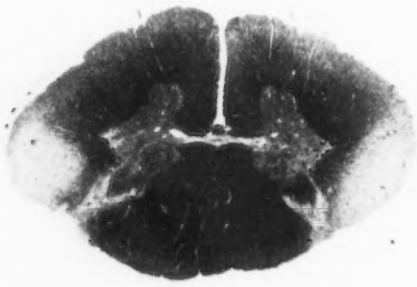

FIG. 10.—Transverse section of the spinal cord showing demyelination of the lateral pyramidal tracts. Myelin sheath stain (Weil modification).

Comments.—This patient, as in Case 1, showed mental symptoms, Parkinsonian facies, rigidity of both upper extremities, absent abdominal reflexes, and pyramidal tract signs. Atrophy of the muscles was not observed. The diagnosis of multiple sclerosis or degenerative disease of the nervous system was considered. The histopathological changes, except for minor differences, were almost the same as in Case 1. The third layer of the cortex was less involved than the fifth and sixth layers, and there was no increase in the microglia cells of the cortex. The temporal lobes showed more marked changes than in Case 1. There was absence of corpora amylacea in the pallidum, and no changes in the corpus Luysii, paraventricular and dentate nuclei. There was no evidence of inflammatory cells in any of the sections. Giant glia cells, as found in Alzheimer's disease or pseudo-sclerosis, were not seen. The pathological changes in the spinal cord were similar to those found in amyotrophic lateral sclerosis.

III.—DISCUSSION.

Review of literature.—Creutzfeld [1] in 1920, and Jakob [2] in 1920 and 1921, described a series of cases which were designated by

Jakob as "spastic pseudo-sclerosis." The disease occurred in middle age or later, and consisted of slowly-developing disturbances of the motor and sensory functions, and changes in personality, as anxiety, irritability, and depression. At first the disease gave the impression of being functional. The patients soon complained of weakness, pain and stiffness of the legs. On attempting to walk, they frequently fell; gait was spastic. The abdominal reflexes were diminished or absent. In most cases remissions occurred. Gradually the motor disturbances became more distinct; there was a mixture of spastic and thalamo-striatal features. At first, gait was incoördinate, and toward the end the patients could neither walk nor stand. Hypotonia of the extremities was observed in some of the cases. Distinct striatal symptoms, such as slow spontaneous movements, rigidity, tremor and athetosis, were outstanding features. The speech was slow, monotonous, and usually dysarthric. The tendon reflexes were usually increased, but in some patients they were normal or even absent; the Babinski reflex in certain stages of the disease was positive. The fundi remained unchanged. The blood and cerebrospinal fluid were normal. Toward the end, the mental symptoms became more marked, and consisted of apathy, negativism, delirium, confusion, visual and auditory hallucinations, and confabulations, which reminded one of Korsakoff's syndrome. Cerebral irritative symptoms, involvement of the bulbar nuclei, decubitus ulcers, marked stupor and fever, brought the disease to an end. The evolution of the disease was comparatively rapid, lasting from several weeks to a year.

Pathologically, this syndrome, as described by Jakob, was characterized by widely disseminated lesions involving mainly the frontal, temporal and precentral convolutions, the corpus striatum, the ventromedial nuclei of the thalamus, the bulbar nuclei and the anterior horn cells. The changes were non-characteristic ganglion cell degeneration, fatty degeneration, swelling, neuronophagia, glia rosettes, outfall of ganglion cells and small areas of devastation (Verödungsherde). There was generalized proliferation of protoplasmatic glia, especially in the last three cortical layers. As a result of the lesions of the giant pyramidal cells of Betz in the precentral gyrus, there was a slight descending degeneration of the pyramidal tracts of the spinal cord.

The clinical diagnosis in all these cases varied between multiple sclerosis, general paralysis, Alzheimer's disease, dementia præcox, and pseudo-sclerosis. At first the disease was considered functional. From the pathophysiological and clinical points of view, according to Jakob,

the disease belongs to the spastic system type, especially amyotrophic lateral sclerosis, and to the strio-pallidal group. Jakob, because of the pyramidal tract signs, designated the disease as spastic pseudo-sclerosis, to differentiate it from the pseudo-sclerosis of Westphal-Strümpell. The giant glia cells (Alzheimer's cells) found in pseudo-sclerosis were not seen in this new syndrome.

Alzheimer [3] (1916) described a case which belongs to the same group. The brain in this patient did not show the marked changes found in the cases of Creutzfeld and of Jakob. There were compound granular corpuscles throughout, and giant glia cells in the globus pallidus which did not resemble those seen in pseudo-sclerosis. Von Economo and Schilder [4] (1920) reported a case which evidently belongs to this group. The striatal symptoms were more prominent, and pyramidal tract signs were absent. In addition to disseminated lesions in the brain (the spinal cord was not examined), the authors described an interstitial hepatitis, and considered a diagnosis of pseudo-sclerosis or Wilson's disease. Stauffenberg [5] in 1918 published a case of olivo-ponto-cerebellar atrophy which may also be placed in the Creutzfeld-Jakob group. Woerkom [6] reported two patients similar to those described by Von Economo and Schilder; in each the liver was involved. Fleishaker [7] (1924) recorded one case with similar findings, but felt that it belonged to the paralysis agitans group. Kirschbaum [8] (1924) also published two cases, and named them spastic pseudo-sclerosis (Jakob).

Each of my two cases had a clinical course somewhat similar to those described by Creutzfeld, Jakob and others. The mode of onset, the age, the absence of obvious cause, the mental changes, the motor disturbances, the absence of the abdominal reflexes, the striatal symptoms and the short duration of the disease were similar. The minor clinical differences consisted in the absence of sensory disturbances in my first case, the absence of remissions, the presence of the Babinski sign throughout instead of in certain stages only of the disease, and the appearance of the mental symptoms late in the course of the disease. Histopathologically the differences were more striking. In my two cases pronounced lesions of the thalamic nuclei, marked neuronophagia and glia rosettes were not found. Giant glia cells, as observed by others, were absent in my cases. None of Jakob's cases showed the new vessel formation in the cortex and pallidum. Microglial proliferation as found in my first case was only observed in Case 1 of Creutzfeld. In contrast to Case 1 and the Creutzfeld Jakob group, Case 2 did not show marked

glial proliferation. None of the authors described calcification of the pallidal vessels and the status demyelinatus of the globus pallidus.

Calcification.—A number of pathologists agree that focal and perivascular calcification occurs wherever there is degeneration. This process has been observed in various conditions, such as epidemic encephalitis, idiocy, carbon monoxide poisoning, malaria and diseases in presenium. Other observers maintain that the deposition of the calcium is a secondary occurrence and that it has no relationship to the pathological process. They point out the fact that the tissue surrounding the calcified vessels remains intact. Hurst [9] has shown that the richness of the globus pallidus in iron is very likely related to a gross and often striking infiltration of its vessel walls by calcium salts, a condition found by him in fifty out of a hundred brains from cases of chronic nervous disorders. Hallevorden and Spatz [10] think that the deposition of the pigment in the pallidum and in the substantia nigra in certain cases is a pathological exaggeration of a condition normal to those structures and indicating a close physiological relationship between them. They regard the pigment as a product of metabolism and attribute its formation to neuroglial nuclei. Urechia and Elekes [11], who found calcification in the vessels of the lenticular nucleus in cerebral syphilis, believe the deposit to consist of fatty acids, iron and calcium. Lhermitte, Kraus and McAlpine [12] found deposits giving an iron reaction in the vessels of the anterior half of the globus pallidus in encephalitis lethargica. Spielmeyer [13] considered the deposition of calcium in the adventitia of cerebral vessels a common change in chronic disease, in old atrophic areas, and also in acute processes such as carbon monoxide poisoning and encephalitis lethargica. Cerebral calcification has been also described by Bassoe and Hassin [14] and by Geyelin and Penfield [15]. The latter is of the opinion that in his cases there was probably a slowly progressive closure of the end arteries in the cerebrum, producing an area of local necrosis, chiefly at the level at which the short pial vessel supply ends and the deeper blood supply begins. This area of degeneration then becomes secondarily calcified, and calcium is laid down in the walls of the vessels. Hadfield [16], in an extensive investigation, concludes that the walls of the blood-vessels of the healthy globus pallidus are often infiltrated with iron salts which are derived from the nucleus itself. He considers the likelihood that the process is one of involutionary atrophy and that it predisposes to the acute bilateral destruction of these nuclei so frequently observed in coal-gas poisoning.

The reports of numerous investigators and the findings in cases of other neurological disorders from this laboratory, suggest strongly that the calcification of the vessels in the globus pallidus of my two cases was secondary to the pathological process. The degeneration in the pallidum, which was due to the same agent as that of the rest of the central nervous system, caused a secondary calcification. The calcium was deposited in the walls of the vessels. The secondary calcification of the vessels leads to further destruction of the pallidum, as evidenced by the marked change found in the pallidal cells, and the status demyelinatus.

Status demyelinatus.—Cécile and Oskar Vogt [17] described under the term "status demyelinatus" a process in which there is a poverty of the white fibres of the striatum, especially those of the pallidum. It starts in childhood and leads to a progressive rigidity. The same process was described in juvenile cases by Fischer [18], Rothmann [19], Hallervorden and Spatz [20], Kalinowsky [21], Fungfeld [22], Onari [23], Lhermitte and Von Bogaert [24], Winkelman [25], and others. Hallevorden and Spatz [20] described the status demyelinatus in five children of the same family, the disease appearing between the ages of 7 and 9. Kalinowsky reported the condition in three sisters in whom the disease began at the ages of 9 to 10. In Fungfeld's case the disease was noticed at the age of 25, and Onari's case, observed at 41, gave a long history of disturbances in speech and gait, and athetotic movements. The demyelination of the white fibres of the globus pallidus in my two cases resembles somewhat the pathological picture seen in the cases described by Cécile and Oskar Vogt and others, but there is no clinical similarity.

Differentiation from other neurological disorders.—As seen from the clinico-pathological descriptions these two cases are closely related to Wilson's disease, pseudo-sclerosis of Westphal-Strümpell, chronic encephalitis, and amyotrophic lateral sclerosis with mental symptoms.

Pathologically, Case 2 showed a normal liver. In Case 1 the liver was not examined as permission for removal of the brain and spinal cord only was obtained. The absence of giant glia cells described by Alzheimer, and the lack of neuronophagia and glia rosettes, definitely rule out Wilson's disease and pseudo-sclerosis, but this differential diagnosis could not have been made clinically. The rapid course of the disease and the total absence of evidences of inflammation, in contrast to some of Jakob's cases which showed in places reactive inflammatory cells, would seem to rule out chronic encephalitis. These two cases were

considered at one time as amyotrophic lateral sclerosis with mental symptoms, but the pallidal symptoms would seem to exclude definitely this diagnosis. The pyramidal tract changes were most likely due to descending degeneration as a result of destruction of the giant pyramidal cells of Betz. In Case 1 the descending degeneration was only observed in the pyramids of the medulla oblongata and in the cortico-spinal tracts of the cord. A primary affection of these tracts, independent of the destructive changes in the giant pyramidal cells of Betz, must also be considered. The changes found in the anterior horn cells were possibly part of the disseminated process found elsewhere in the nervous system. Multiple sclerosis, although considered in these cases, as well as in those described by Creutzfeld and by Jakob, was definitely ruled out as the disease progressed. Pathologically the process was not at all related to multiple sclerosis.

IV.—Summary.

A disease of comparatively short duration occurring in two adults without any demonstrable ætiology and presenting mental changes, pyramidal tract signs, absent abdominal reflexes and striatal symptoms, is described. Pathologically there was atrophy of the cerebral convolutions from the frontal to the parietal regions, scantiness and destruction of the ganglion cells in the third, fifth and sixth laminæ with areas of devastation, proliferation of glia and vessels, degeneration of the pyramidal tracts, calcification of the vessels of the pallidum, status demyelinatus of the pallidal fibres, and changes in the anterior horn cells of the spinal cord. The name "disseminated encephalomyelopathy" is descriptive of the clinical syndrome and its pathology, but for the present it is advisable to adopt Jakob's title, Spastic Pseudo-sclerosis.

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THE DIFFERENTIATION OF BEHAVIOUR PATTERNS IN THE FŒTUS AND INFANT.

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THE first appearance and development of behaviour patterns form an important subject for study with practical application as a basis for the understanding of the more complicated reactions of the adult. From the experimental point of view the problem offers considerable difficulties in the case of most mammals, inasmuch as the fœtus must be removed from the uterus and observed under very artificial conditions where proper oxygenation of the blood is almost impossible. This latter objection applies especially to the study of the human fœtus of the second to the sixth month where the umbilical cord must be severed before the observations are begun. Obviously the fundamental work must be done upon forms lower than mammals where the organism has an independent blood-supply from the beginning, or upon mammals which are born very immature after a short gestation period. The first of these methods has been used by Coghill, who formulated in this way general principles of behaviour development which appear to hold also for mammals. The second method has been used by the author, inasmuch as he obtained a very suitable mammal for study, the opossum.

Coghill was exceedingly fortunate in his choice of an experimental animal, *Amblystoma punctatum*, an example of the amphibian Urodela. In this form the tail is not absorbed in metamorphosis from the tadpole to the adult condition, but the trunk and tail continue throughout life as a flexible, integrated organ, the bending of which gives the animal its power of aquatic locomotion and subsequently becomes the primary factor of locomotion on land.

The opossum (*Didelphys virginiana*), a marsupial, is born after a ten-day gestation period, when scarcely more than one centimetre long. The young is able to crawl into the pouch by seizing the hair of the mother with the claws of the fore-leg and pulling itself along. The distance covered in this journey is, of course, short. When it has reached the pouch it seeks for and becomes attached to a nipple. The

nipple is swallowed far down in the pharynx and the young remains attached for weeks without relinquishing its hold. The movements of the animal in the pouch appear to be few, and certainly the field of activity is very circumscribed. At this time the skin, covered by no coat of fur, is pink and wrinkled, appearing too large for the animal; it is also thin and transparent, so that structures underneath are visible. The fore-legs are relatively large and muscular with well-developed claws; the hind-legs are mere buds and show very little differentiation. The tail is as long as the fore-legs. No vibrissæ are present on the face; the lateral mouth grooves have not developed and the mouth appears as a round hole. The eyes are not open, in fact no eye-slits have yet appeared. The pinna of the ear is just developing from the underlying skin. Inasmuch as the form of the body organs is not yet complete, these may be considered as embryonic preparations.

There remains to consider the observations of human fœtal preparations made by Minkowski and others. Perhaps the total number of specimens studied is now over fifty. Minkowski was fortunate in that he was able to examine a number of fœtuses removed at hysterectomy which was performed under local anæsthesia. The specimens were, therefore, not anæsthetized, and must have been much more active than those obtained at operation when a general anæsthesia is used. The fœtus was immediately placed in a bath of physiological saline heated to 37° C.; observations could often be continued for as long as two hours. The umbilical cord was severed when the fœtus was obtained, and the preparation must be considered as asphyxiated from the very beginning of the observations. However, it is permissible to accept the findings in so far as they agree with those obtained from other animals in which the oxygenation of the blood is more perfect. The discussion of the observations will be considered under topical headings representing general principles of development of behaviour patterns with the evidence obtained from the work just described.

Coghill showed that the first reflexes represent the total activity of the organism. The behaviour pattern from the beginning expands throughout the growing, normal animal as a perfectly integrated unit, whereas partial patterns arise within the total pattern and, by a process of individuation, acquire secondarily varying degrees of independence. In the development of the individual the earliest reactions are generalized, and it is only later that specific behaviour patterns develop out of this generalized reaction. Complexity of behaviour is not derived from the progressive integration of more and more originally discrete units.

Partial patterns emerge and tend toward independence and dominance, but always remain under the supremacy of the individual as a whole.

In the case of the amblystoma, this may be illustrated by the development of the reflex for progression. The first movements are made by the most anterior part of the muscle system of the trunk. They consist of a bending of the trunk to one side or the other. As the animal grows older, this flexion extends farther and farther tailward. These movements gradually increase in speed, and, in this way, acquire locomotor value. A flexion of the body in one direction followed by a flexion in the opposite direction produces swimming. When the legs have developed the primary component of walking is a slow, swimming movement of the trunk and tail which involves the limbs. The fore-legs are integrated with the movement of the anterior portion of the trunk, and the spread of the trunk movement to the region of the hind-legs involves them in movement. Accordingly, the hind-legs do not move synchronously with the fore-legs, but lag behind them by the interval required for the trunk flexure to spread from the fore-leg to the hind-leg.

Hartman (1920) observed and described the birth of the opossum. The adult female first showed signs of restlessness and began cleaning the pouch, which she did about four times. Then began a series of spontaneous contractions of the abdominal wall, after which she came to a sitting posture with legs extended, body bent forward, and began to lick the vulva. Suddenly a tiny bit of flesh appeared at the vulva and scampered up over the entanglement of hair into the pouch. Unerringly the embryo travelled by its own efforts; without any assistance on the mother's part, other than to free it of membranes and liquid on its first emergence into the world. This ten-day-old embryo is able, immediately upon its release from a liquid medium, to crawl a full three inches over a difficult terrain. Indeed, it can do more: after it has arrived at the pouch it is able to find the nipple amid a forest of hair.

The adult female was then etherized and the interior of the pouch examined. It contained a squirming mass of eighteen red embryos, of which twelve were attached, although thirteen might have been accommodated. The remainder were, of course, doomed to starvation. Some of these held on with their mouths to a flap of skin or the tip of a tail, while several continued to move about.

Hartman gently pulled off a number of embryos from the nipples. The teats had already been drawn out from about a millimetre in height to double that length, doubtless by the traction of the embryo itself.

One detached young, placed near the vulva, crawled readily back into the pouch. Two or three others regained the teats after some delay, while one wanderer found a vacant teat and attached itself after twenty minutes. If the skin be tilted, the embryos can be made to travel upward and even away from the pouch, for they are negatively geotropic. For locomotion the embryo employs a kind of "overhand stroke" as in swimming, the head swaying as far as possible to the side opposite the hand which is taking the propelling stroke. With each turn of the head the snout is touched to the mother's skin, and the embryo stops at once when the nipple is reached.

Goerling (quoted by Hartman) saw a new-born kangaroo clinging to the long hair about 4 in below the opening of the pouch. It moved about very slowly, pushing its way upward through the hair. The head moved continually from side to side. Nearly thirty minutes were required for the little wanderer to reach the top of the pouch. During the whole of this time the mother paid no attention to her offspring, offering no assistance and leaving it to its own exertions.

Several young opossums, seven days old and 27 mm. in length, were removed by the author from the pouch for study. They were very active but helpless to cope with the environment outside the pouch. The opossums always lay on the side and never with the ventral surface of the body downward. The persistent flexion of the trunk prevented them from assuming this posture. The muscular contractions were widespread and consisted of contractions of the abdominal trunk musculature, causing a curving of the body with a bowing of the back. Beats of the fore-legs occurred but there was little contraction of the hind-leg musculature. It is evident that the first contractions of the musculature of the opossum involve the trunk and abdominal musculature and are very diffuse.

A pattern has, however, already grown out of this mass contraction of the body musculature, useful in that it enabled the animal to reach the pouch. If an opossum was placed upon a piece of gauze so that the claws could gain a hold, the claws of the fore-legs seized the threads and the young pulled itself along by alternate progressive movements of the fore-legs. The fore-leg contractions were not yet precisely co-ordinated units, but they were associated with contractions of the whole trunk musculature. The musculature was so strong that the young animal could support the weight of the body hanging by one fore-leg. It was only later, with the functioning of the vestibular mechanism, that the young animal could right itself upon a smooth surface and

remain with the ventral surface of the body downward. With the differentiation of the hind-legs their movements become co-ordinated with each other and with the fore-legs.

In the human fœtus of two to six months the diffuseness of early motor responses is seen again. Minkowski found that it was not possible to obtain isolated reflexes but very generalized and variable motor reactions. For example, stimulation of the foot may produce, in addition to a withdrawal of the knee, motor reactions in both arms, the head and trunk. Stimulation in the region of the eye produced a contraction of the orbicularis muscle and movements of the legs in a fœtus, 6·5 cm. in length.

Even the new-born human infant responds to stimuli with widespread motor responses which spread and increase in intensity with the strength of the stimulus. It is only later, as differentiation from the response of the organism as a whole, that refinement and delicacy of activity evolve.

The sensory field of the reflex and the field of motor response are at first diffuse. The first response of an amblystoma to any tactile stimulus is a contraction of the musculature of the opposite side of the trunk. Similarly, when the young opossum is placed upon a table for inspection, touch, heat or pin-prick serve to increase the widespread contractions of the body musculature.

This is particularly well illustrated by the development of the plantar reflex in the human fœtus and infant. At first the field from which this reflex can be obtained consists of the entire leg, and the response is equally widespread, consisting of movements of the toes and flexion of the ankle, knee and thigh. The opposite leg may also take part. Gradually, with further development, the sensory field for the response becomes limited to the plantar surface of the foot and only the toes take part in the reaction.

The gradual limitation of motor and sensory responses is due to the development of inhibition in the nervous system. In early development an adequate impulse carried into the nervous system is diffused widely to all motor cells; later the pathway becomes limited. The early response is seen in the adult after transection of the spinal cord when the isolated segments have become active. Then a sensory stimulus applied to a portion of the body innervated by the isolated cord produces a mass contraction of all the musculature innervated below the lesion. The reflexes have lost their local sign and a sensory impulse spreads widely, giving a mass reflex. The inhibitory control of the brain has been removed.

Activity in the spinal cord first develops in the cervical portion and progresses caudally; in the brain it begins in the medulla and progresses in a cephalic direction. Coghill observed that the first movement of amblystoma in response to stimulation occurred in the cervical region and, with development, gradually the movement spread farther and farther caudally. The response was a contraction of the myotomes on the opposite side of the body producing a curvature of the body away from the point of stimulation. No response could be obtained until definite anatomical circuits had been laid down in the nervous system. The sensory neurones at an early period of development have no local reflex connection with the anterior horn cells of the same segments, but communicate with commissural fibres at the level of the fifth myotome which carry the impulse to the opposite side of the cord. Gradually commissural neurones are developed in more caudal segments.

The opossum shows reflex activity of the fore-legs which is well co-ordinated at a time when the hind-legs are relatively undifferentiated. It is much later that patterns of reflex activity appear in the hind-legs. It might be said, of course, that the case of the marsupial is unique among mammals in that precocious development of the fore-legs is required to enable the young to reach the pouch. In kittens also the fore-leg movements become co-ordinated before those of the hind-legs. Study of the anatomical development of the spinal cord, using myelinization of nerve fibres as a criterion, shows that medullation begins in the cervical portion of the cord and continues in a caudal direction.

As regards the brain, maturation first occurs in the medulla in the areas controlling respiration, deglutition and the orientation of the body, and gradually spreads cephalad through the mid-brain, thalamus and cerebral cortex. This is demonstrated in the human fœtus and newborn, using myelinization as an index of maturation. The vestibular mechanism and associated structures in the medulla develop very early, and when they begin to function the organism becomes oriented in respect to the environment.

Reflex patterns arise within the picture of total activity of the organism. When the legs are first developed in amblystoma they function with the total reflex activity of the trunk musculature without any local reflex modalities of their own. Later patterns of activity involve the leg musculature alone. Thus, from and within the total activity of the organism, patterns of movement are laid down in restricted groups of muscles; these patterns are always subservient to the total activity pattern of the individual. The same phenomenon was

observed in the opossum. The first activity undoubtedly consisted of contractions of the whole trunk musculature producing the squirming and twisting movements in which the fore-legs participated. Later, the fore-legs developed more circumscribed and precise movements in which the claws seized the hair and alternate movements of the fore-legs pulled the animal along.

The differentiation of reflex patterns is also observed in the studies of the human fœtus. Minkowski obtained a reflex on stimulation in the region of the mouth in a fœtus of 3·5 cm. Opening and closing of the mouth were associated with movements of the legs; the reflex pattern involved the motor system from the level of the trigeminal nuclei to the caudal portion of the cord. Opening and closing of the mouth as a purely local reflex occurred in an infant of 21·5 cm. It would appear that the oral reflex in response to touch first appears as a part of a larger pattern of movement and only later is differentiated as a distinct reflex.

One of the first reflex patterns developed is the escape reaction. Coghill early observed that the first reaction of amblystoma has the qualities of an avoiding reaction. Thus, a stimulus applied to the body produces a strong contraction of the muscles of the opposite side; this reaction carries the organism away from the stimulated point. Escape reactions may be elicited early in mammals. Stimulation of the foot-pad of one hind-leg of the kitten produces withdrawal of that leg and withdrawal of both hind-legs if the stimulus is of considerable intensity. Perhaps the diffuse and rather violent movements of the fœtal preparation may be considered escape reactions.

Many of the earliest reflexes to develop do not, in themselves, appear to be of value to the organism. The grasping and hanging reflex observed in the human new-born infant would appear to be of no value to the infant; it is believed to be a survival of a mechanism observed in many primates by which the young are able to hold to the hair of the mother and thus are carried safely. The tail of the opossum becomes prehensile and can even support the weight of the body a considerable time before the animal leaves the pouch.

In the human subject many of the earlier developed reflexes are soon completely inhibited. This is true of the grasping or hanging reflex and also of the sucking reflex. It would appear that they become incorporated in other more complicated reflex patterns. The grasping reflex is lost at the time when the infant begins to reach out voluntarily after objects placed within its reach. Under certain conditions, such

as intoxication with drugs, organic lesions of the brain or in the insane, the hanging reflex may again appear in adults. Similarly, the sucking reflex early becomes conditioned, but it may sometimes be demonstrated in the old or insane.

In amblystoma, a time occurs in development when the first response to sensory stimulation, the avoiding reaction, may be obtained. Coghill points out that this first response cannot be determined in its origin by previous responses, or modified by experience or exercise. The sensory pathways and their connections in the nervous system are laid down before the sense organ differentiates and functions, so that responses are limited to anatomical pathways already formed.

In order to understand the development and growth of behaviour patterns in mammals, it is necessary to account for their differentiation from the diffuse total pattern of activity before the birth of the animal. Bok's hypothesis of the circle reflex, particularly as elaborated by Holt, gives an explanation for the development of early specific reflexes.

First, it must be assumed that sense organs may be stimulated *in utero*, and that many sensory stimuli continually enter the central nervous system from proprioceptive endings in the muscle, from the skin and from certain special sensory organs. Indeed, in the case of the human subject, it is probable that all types of sense organs may receive adequate stimuli in the uterus except the olfactory and optic. The proprioceptive sensory apparatus is probably one of the earliest to function.

When a sensory stimulus enters the nervous system, it spreads widely and produces a diffuse motor response of the striated musculature. For an example, the biceps muscle contracts in this generalized response, involving also many other muscles. The contraction of the biceps stimulates the proprioceptive endings in the muscle itself, which in turn send impulses to the nervous system. Inasmuch as these sensory fibres have the closest anatomical relationship in the cord with the motor cells innervating the biceps, and inasmuch as the sensory impulses from the muscle reach these cells before the initial contraction is complete, the secondary influence tends to reinforce the first contraction. In this way a circle reflex is set up and becomes, in time, active continuously. Stimuli from proprioceptive endings in a muscle influence the anterior horn cells which continually send stimuli to the striated muscle. Throughout the life of the individual, tone in a muscle is dependent upon proprioceptive impulses arising continually in the muscle itself. If this reflex arc is broken on the efferent side, all tone is lost in the striated muscle.

The theory of the circle reflex may be used to explain the development of any of the early reflex patterns. Take, for example, the grasping reflex. Here the diffuse motor response may involve, in particular, the flexor musculature of the fore-arm and cause the fingers to press tightly against the palmar surface of the hand. Stimuli are then set up in the nerve-endings of the palmar surface of the hand or flexor surface of the fingers, both in superficial and deep structures, which tend to augment the contraction of the flexor muscles, inasmuch as the secondary stimuli reach the motor cells of the cord before the first contraction is complete. Thus a new circle reflex becomes established and any stimulation of the flexor surface of the hand produces the grasping reflex. With the development of function in the cortico-spinal pathway in the young infant, the grasping reflex is taken over by voluntary cortical control to be used in reaching and seizing objects. It it only under abnormal conditions that the primitive reflex again appears in adult life.

The first reflex patterns to develop, such as the reflex producing tonus in the muscles or the grasping reflex, are controlled by segmental or intersegmental reflex mechanisms. These reflexes are later modified, as has just been suggested, by influences from the brain ; the tonus of an individual muscle comes under vestibular influence and becomes a part of a pattern of tonus, and the grasping reflex becomes a part of voluntary reaching.

Minkowski, in the case of the plantar reflex, has endeavoured to follow the development of control from different portions of the brain over segmental reflexes. The first stage he calls the embryonic or transition stage ; it appears during the second month of fœtal life. The reaction to stimulation of the dorsal surface of the foot is characterized by its inconstancy and variability. Sometimes a dorsal flexion of the toes occurs, followed by a plantar flexion. The reaction may be reversed during the course of the observation. It appears at a time when there is a transition from an ideomuscular response to a control of the muscle by the nervous system. The reflex through the nervous system is as yet inconstant and labile. The response is obtained only under particularly favourable conditions and after only a small proportion of the stimuli. Its form is determined each time by the state of excitability and conductivity of the corresponding segments of the cord.

The second stage of development is called the early fœtal or spinal stage ; it can be elicited in a fœtus from 5 to 13 cm. in length, corresponding to the third or fourth month of fœtal life. The dorsal flexion

of the toe predominates at this time over plantar flexion, bu tthis predominance is only relative and is seen only under favourable conditions. During the course of the observation the extensor reflex may change to flexion. This response is believed to be controlled entirely by spinal centres and is uninfluenced by cutting the spinal cord in the cervical region.

The third stage is called the tegmento-spinal stage. The preparations in which this can be demonstrated are from 16 to 30 cm. in length and four to six months of age. At this period it is the dorsal type of response which predominates. The reactions show all the types of variation seen in the clinic, such as dorsal extension of the great toe alone, spreading of the toes or extension of the toes of the opposite side. Sometimes, after a period of the reflex in extension, plantar flexion is seen, with or without participation of the great toe; this is the phenomenon of inversion. At this period the great toe may not only flex but also oppose the other toes, giving the prehensile reflex which is found regularly in the monkey. Flexing of the whole leg may accompany extension of the toes.

This phase of the plantar reflex cannot be considered to be controlled entirely by the spinal cord but is dependent on supraspinal factors. Section of the cervical portion of the cord is followed by a transitory period of shock and of areflexia. Then a plantar type of response is frequently produced. The plantar reflex is now under the influence of a supraspinal factor which favours dorsal flexion; this control lies in the medulla. The reticulo-spinal tract and medial longitudinal fasciculus are now beginning to influence the activity of the anterior horn cells.

It is not proposed to consider the other four stages in the evolution of the plantar reflex which Minkowski described, ending with the control of this reflex by cortico-spinal influences in the normal child over 2 years old. This illustration suggests a method that may be used in further studies of the development of control by the brain over early segmental and intrasegmental reflexes.

Tonic and postural reflexes appear very early in the differentiation of the nervous system. Coghill observed that postural reflexes could be observed in the legs of the amblystoma before any isolated reflexes, apart from generalized movements with the trunk. The newborn opossum lies upon the side with the whole body flexed ventrally. Even at this time postural reflexes are active in the fore-legs, for if the claws are allowed to grasp the threads of a piece of gauze, the body can be

oriented in such a way that effective alternate movements of the fore-legs may occur.

Minkowski found that in the human fœtus of two months, tonus in the musculature of the extremities maintained them in a determined position, and returned them to that position after they had been passively moved. Tonic reflexes produced by changes in the position of the head in relation to the trunk and labyrinthine reflexes were obtained from the fœtus of the third or fourth month.

Graham Brown (1914) showed that, under certain conditions, even in adult life, the anterior horn cells of the cord may react to substances carried in the blood-stream after the manner of the respiratory centre. Herein lies the difficulty of observations upon fœtal preparations after the umbilical cord has been tied and no respiratory reflexes are active. Asphyxia gives rise to diffuse motor stimulation.

It is also possible that the first motor reactions of the fœtus occur in response to blood-borne stimuli. This implies that the motor side of the reflex arc becomes receptive before the sensory side. There is some slight evidence that the motor cells are mature before the sensory. In the spinal cord the motor roots are myelinated before the sensory. To use these data one does not need to assume that nerve fibres become myelinated at the time when they become functional, but only that fibres become myelinated in the order in which they become functional. Then activity would begin upon the motor side and the circle reflex develop with the first responses of the sensory portion of the reflex arc.

The first motor responses in response to sensory stimulation are diffuse. Anatomically, it is clear that the sensory neurones which enter the cord branch many times and establish countless numbers of reflex connections. By the mechanism of the circle reflex patterns of behaviour are developed. This implies that certain connections of the sensory fibre in the nervous system have become inhibited so that diffuse responses no longer occur. Inhibition in the caudal half of the spinal cord, even in adult life, is evidenced by the mass reflex which follows transection of the spinal cord in the thoracic region.

Pavlov believed that conditioned reflexes were all dependent on the cerebral hemisphere. Krasnogorski (1909 and 1913) has studied the development of conditioned reflexes in the child, and found that the mechanism for association does not appear until the second half of the first year, and is not functionally complete until the second year. He believes that associations are more readily extinguished in children than in dogs.

There is much evidence that conditioning occurs in the human infant at an earlier age. In the newborn, the sucking reflex is very active and may be obtained by placing the finger on the lips or even touching the cheek. Non-specific responses disappear during the first few weeks; the sensory area for sucking becomes specific for special types of lip stimulation. The child early becomes conditioned in respect to food. It will reach for the bottle by the one hundred and twentieth day and, even before that time, movements of the arms and legs are increased when the bottle appears. The functions of elimination can be conditioned from the second week on; it becomes a matter of only a little care to condition them after the third month.

Indeed, the development of the earliest reflexes of the fœtus show many analogies with the conditioned reflexes. Gradually the sensory locus and the motor response become circumscribed and purposeful, due to the inhibition of disturbing extraneous factors. The mechanism of differentiation of all behaviour patterns does not differ from that effective in the production of the conditioned reflex.

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Notices of Recent Publications.

Reflex Activity of the Spinal Cord. By R. S. Creed, D. Denny-Brown, J. C. Eccles, E. G. T. Liddell and C. S. Sherrington. Pp. 183. Oxford: Clarendon Press. 1932. Price 10s.

Some ten years ago Sir Charles Sherrington introduced a new technique to the study of reflexes, and already a large literature has arisen from the results yielded by it and the new interpretation of spinal reflexes thereby derived. The essential feature of this new technique is an instrument called the "Isometric Torsion Myograph," by which reflex muscular contraction can be measured quantitatively, and consequently the relative numbers of motor nerve-cells involved in different reflexes deduced. By improved electrical methods the rate of discharge of motor neurones can also be ascertained.

In a small volume Sherrington and four of his co-workers have summarized the present position of the subject, presenting the accumulated evidence upon which the newer conceptions are based, and defining the many technical terms which make the reading of any modern contribution to the subject very difficult for one unfamiliar with its development.

Since the publication of the "Integrative Action of the Nervous System" in 1906, the broad outlines of spinal reflex physiology there defined remain fundamentally unchanged. Knowledge more especially of the intimate details of central excitation and inhibition has deepened, and has been applied with considerable success to the elucidation of the postural reflexes underlying muscle tone, and with more confidence the physiologist speaks of nerve cells and their discharge rather than in broader terms of reflex response.

The means by which afferent impulses cause neurone discharge have been explored in a variety of ways. The series of nerve impulses which an anterior horn-cell discharges in the course of its activity, and the way this scheme is affected by natural condition, now rests on a working hypothesis of "the central excitatory state." At the anterior horn cell incoming afferents converge to bombard the cell surface with excitatory or inhibitory effect. The motor-cell does not discharge unless a certain threshold of afferent bombardment occurs. Large numbers of motor neurones are affected in every reflex, but only a proportion of them discharge, so that there are widespread "subliminal fringes" to each reflex, and the variable reinforcements of these form the basis of co-ordination. The way in which afferent impulses of light function mutually interact, and the consequent variations in the number of motor cells brought to discharge are described. The tendon-jerks record more faithfully the

fluctuations of the spinal centre than was ever suspected by those who at one time would have called the knee-jerk a muscular phenomenon and not a reflex. Although the rigorous fixation of the origin and insertion of the muscle by drill and clamps makes the isometric method impracticable for use in recording human reflexes, yet the elucidation of the stretch reflexes and their interactions explains many of the curious reflex phenomena in spastic patients.

The book has no pretensions as a clinical manual, nor does it attempt to describe reflex phenomena in man. The principles of reflex action are, however, of prime importance to those interested in clinical reflex changes.

Cytology and Cellular Pathology of the Nervous System. Edited by WILDER PENFIELD. New York: PAUL B. HOEBER. 1932. Pp. 1,267. (3 vols.) Price $30.

This work is planned on the same lines as the well-known series of volumes on Cytology edited by Professor Cowdry, to which it may be considered supplementary. Its aim is to present a full and clear description of the various structures which make up the nervous system, including the peripheral end organs and the retina, and to give some indication of the alterations which they undergo in disease. As is to be expected in a work on cytology, normal appearances are more fully described than pathological changes; but this is an advantage to the neurologist, who is apt to be so attracted by the abnormal that he fails to obtain a thorough knowledge of the normal. It is true that a few chapters in the third volume are devoted entirely to pathological conditions, but these only attack a small sector of the field of neuropathology. The chapters on hydrocephalus and on tumours of the brain, the spinal cord and the eye are useful synopses of recent work. But undoubtedly the most valuable chapters are those in which the editor's own pioneer work is summarized. These have a strongly individual and often unorthodox bias which, to the reader, is always stimulating, albeit occasionally somewhat confusing. It has been the editor's object to include contributors of all nationalities and chapters have been written by Ariëns Kappers on neurobiotaxis, by Boeke on nerve-endings, by Bielschowsky on the histopathology of nerve-cells, by Nageotte on the peripheral nerves, and by Del Rio Hortega on microglia. These will ensure for the book a wide popularity. But many of the chapters contributed by American authors are not less important, Those by Cowdry on the neurone, by Penfield on the neuroglia, by Cobb on the cerebrospinal blood-vessels, and by Weed on the meninges are records of pioneer work of the highest value.

The high price of the book is explained and largely offset by the richness and excellence of the illustrations. Unfortunately the beautiful printing is marred by bad proof reading. Almost every chapter contains a gross printer's error, and in some they are to be found on nearly every page. We hope that a second edition may afford the opportunity of removing this blemish.

Handbuch der biologischen Arbeitsmethoden. Herausgegeben von E. ABDERHALDEN. Abt. V. *Methoden zum Studium der Funktionen der einzelnen Organe des tierischen Organismus.* Teil 7, Hft. 8, S. 995-1,073. Berlin: Urban and Schwarzenberg. 1932. Price 10 Rm.

Previous sections of this comprehensive laboratory handbook have been noticed in this Journal. The present volume contains chapters describing the investigation of tone appreciation, the investigation of labyrinthine functions in reptiles, amphibia, fishes and cyclostomes, and a chapter on the sensory functions involved in the method of palpation.

Hausmann, the author of the last-named article, has confined himself wholly to German sources in his review of the literature. No balanced statement of so difficult a subject can come from so arbitrarily circumscribed an outlook, and the article has therefore the limitations to be expected.

Intracranial Tumours. By HARVEY CUSHING. Pp. 150. Baltimore: C. C. Thomas. 1932.

At the recent meeting of the International Neurological Congress at Berne, Cushing presented a review of the percentage mortality of his operations on cerebral tumours, based on a series of 2,000 cases treated during the past thirty years, in which the natures of the tumours were verified by histological examination. This volume is an amplification of this presentation. The so-called "tumour-suspects," of which there were over 1,000, and cases in which the existence of a tumour was not confirmed by microscopical examination, almost as numerous, are not included in this summary. The tumours are classified according to their structure, the gliomata being subdivided into the types described by Bailey and Cushing, and each type is dealt with separately: in most instances a few case histories are published to illustrate their main clinical and surgical features. The histology of the growths is not described, but references are given to sources where the reader can easily find full descriptions.

But the main interest of this monograph lies in the results of operative treatment. These are carefully tabulated for each type of tumour, as well as for the whole series, for each of the thirty years which cover Cushing's work. As in many instances two or more operations were performed on the same patient, percentages are given separately for the case mortality and the operative mortality. These figures refer, however, only to the fate of patients during their stay in hospital, which averaged thirty-nine days; they deal therefore only with immediate mortalities following operation, and unfortunately give no information on the final results of surgical treatment. The author emphasizes the difficulty in following up and determining the fate of all patients, but it is regrettable that the later results of even a small number of unselected cases of each type are not furnished, for the ultimate prognosis is a

matter of much greater importance to the physician and to the patient than the risk of operation, and there are at present no adequate figures available to show what is the prospect of life in, for instance, the gliomas, by far the commonest of cerebral tumours. This side of the picture is at the most only hinted at, as by the confession that 100 per cent. of malignant gliomata end fatally, and that in astrocystomas for instance, recurrences may be expected within six to nine months.

But the most interesting feature of this monograph is the tables which show the gradual lowering of operative mortality during the past thirty years, which during the last ten years varied between 11 and 15 per cent., and in the last year under review fell considerably lower. The factors which contributed to this improvement are mentioned, but no detailed description of operative procedures are given in this book.

Spezielle Chirurgie der Gehirnkrankheiten. Von FEDOR KRAUSE. Bd. 2. *Die epileptische Erkrankungen.* Part 2. Stuttgart: Ferdinand Enke. 1932. S. 957. Price 63 Rm.

The previous volume dealing with the various clinical aspects of epileptiform seizures has already been noticed in a recent number of *Brain*. The present volume contains chapters devoted to the differential diagnosis of epileptiform seizures from hysterical and other seizures, to the ætiology of fits, and to the localizing diagnosis of focal brain lesions. It is, however, for the chapters dealing with the operative treatment of cases presenting epileptiform attacks that the work will be chiefly valued. Every aspect of cranial surgery is comprehensively discussed, the surgery of intracranial tumours and of traumatic brain lesions being equally considered, and the book will become a standard work of reference for neuro-surgeons. There are very numerous and excellent illustrations.

Beiträge zur Physiologie des Hirnstammes. I. Teil. *Die Methodik der lokalizierten Reizung und Ausschaltung subkortikaler Hirnabschnitte.* Von W. R. HESS. S. 122. Leipzig: Georg Thieme. 1932. Price 24 Rm.

To Horsley and Clarke we owe the construction and employment of the first instrument of precision for the electrical stimulation of determined sites within the brain, and for the production of accurately localized, deep-seated, focal lesions. For the use of this stereotaxic instrument accurate maps of coronal and sagittal sections of the brains of the cat and of *Macacus rhesus* have been drawn up.

Horsley and Clarke used the instrument for investigations into the cerebellar nuclei, and subsequently Mussen in Baltimore and Barrington in this country have employed it.

However, the instrument is complicated and costly, and requires a high

degree of technical skill in its employment, and consequently it has not been so widely employed as its accuracy and usefulness deserve.

Professor Hess has sought to achieve the same end by a new and somewhat simpler apparatus, which is described in complete detail in his monograph, and he has drawn up an atlas of the cat's brain in conjunction with which it can be used. His method appears to have certain advantages of simplicity and ease of employment, but it is not possible for one who has not used both instruments to compare its accuracy with that of Clarke's stereotaxic instrument.

A Textbook of Neuro-anatomy. By ALBERT KUNTZ. Philadelphia: Lea and Fibiger. 1931. Pp. 359. Price $5.50.

The value of a new textbook on the anatomy of the nervous system depends on its simplicity of presentation or its completeness for purposes of reference. In the present book the author makes no pretence to fulfil the latter criterion, claiming rather to have in view the needs of the student "in his first attempts to gain some knowledge of the anatomy and physiology of the nervous system." On the whole it succeeds fairly well, although its method is somewhat unorthodox. For example, the appearances of the spinal cord on external examination and on cross-section are described in Chapter II, its structural arrangement and cell systems in Chapter VIII, and the disposition of its tracts and fibre-systems in Chapter XII. The separation of the description of different constituents of the same organ may be justified on logical grounds, but its didactic value is doubtful.

While some chapters, for example that dealing with the cerebral cortex, have been brought well up to date, others, such as those on the cerebrospinal pathways, on the diencephalon and on nerve-endings are distinctly old-fashioned, and contain several statements which are contrary to modern teaching.

The book is fully illustrated, the best illustrations being borrowed from other textbooks. Of those that are original, the diagrams appear unnecessarily complicated and the photographs of the Weigert-Pal sections of the brain-stem are poorly reproduced from badly-stained sections, and show little that is not visible to the naked eye in fresh specimens.

Taken as a whole the book gives little that is not equally well presented elsewhere, and neglects many points that are of clinical significance.

La Syringobulbie. Contribution à la physiopathologie du tronc cérébral. Par N. JONESCO-SISESTI. Pp. 391. Paris: Masson et Cie. 1932. Price 70 fr.

From his own large experience and from a comprehensive survey of the literature on the subject, the author describes the clinical features and the pathological characters of Syringobulbia. He brings out in his description many interesting points to which perhaps due attention has not been paid, as

the considerable proportion of cases in which the symptoms set in abruptly, or even in an apoplectiform manner, with headache, vomiting, vertigo, disturbances in articulation, phonation and deglutition; such acute attacks may recur in the course of any case. The description of the anatomical lesions is excellent and well illustrated.

But the most important section of this monograph is the analysis of symptoms and their correlation with such lesions as are found in syringobulbia, and the physiological deductions made from the symptoms observed. The diplopia which occasionally occurs is attributed to upset of the labyrinthine apparatus, hiccoughing to irritative lesions of the subependymal vegetative nuclei, and the mental symptoms occasionally associated with the disease to disturbances of the neuro-vegetative centres of the bulb. Such conclusions may not be generally accepted, but the author's conclusions on the functions of the bulbar cranial nerves may be useful in stimulating a re-investigation of views which have been for long accepted as established.

Fleckfieber und Nervensystem. Von N. Hirschberg. S. 124. Berlin: S. Karger. 1932. Price 11.60 M.

Though typhus fever has practically disappeared from Western Europe, the subject of this monograph is of interest at the moment in view of the nervous lesions which have occurred in recent outbreaks of other infections, as measles and smallpox. The author has had a large experience of this disease in Moskau, but unfortunately his book is mainly a review, and not always critical, of the literature of the nervous complications of typhus. He does not furnish any personal pathological observations and therefore fails to present a satisfactory discussion of the nature and cause of the various nervous symptoms which occur. The chapter on the pathological anatomy is merely a summary of old and more recent observations in which the reader receives no critical help from the author.

Les Troubles du Sommeil. Par H. Roger. Pp. 206. Paris: Masson et Cie. 1932. Price 20 fr.

In his first chapter the author describes the special features and the nature of normal sleep, and the many theories which have been put forward to explain it; he assumes that the parasympathetic system, the cerebrospinal axis and mind acting together determine it. The second chapter deals fully with the varieties of insomnia and their treatment, and the third is devoted to the hypersomnias, which are divided into two classes, pathologically prolonged sleep and narcolepsy. But the final chapter on the various qualitative disturbances of sleep, included by the author in the term parasomnia, which are so often neglected by writers of textbooks and monographs, is perhaps the most interesting and important in the book. The lucidity of the style and the practical point of view from which it is written make the small monograph readable and useful.

Probleme der klinischen Psychiatrie. Von KURT SCHNEIDER. Leipzig: Thieme. 1932. S. 46. Price Rm. 2.60.

This is an admirably lucid, brief examination of the broad problems of clinical psychiatry. While so many consider the minute investigation of a particular aspect of psychopathology to be the only profitable study, this wide examination of the problem has especial value. An excellent instance of the author's attitude is in his temperate criticism of the doctrines of Kretschmer and of Kleist. The book is small, and is so interesting that most readers will finish it at a sitting and then return for closer consideration; most of the tendencies in modern German psychiatry are reviewed in it with appreciative sharpness.

Constitution-Types in Delinquency. By W. A. WILLEMSE. With 32 plates and 19 diagrams. London: Kegan Paul. 1932. Pp. 266. Price 15s.

Dr. Willemse has examined a number of delinquent youths as to their physical and mental constitution, using in the main the methods and criteria of Kretschmer. He has endeavoured to bring into relation the attributes of the various types and the form of the delinquency. He has also attempted to co-ordinate the types delimited by Kretschmer with those of Jaensch and others. The author has read enormously rather to the detriment of his book, but as he is desirous of making these writers better known, the defect of readability which results from his undiscriminating citation may be a conscious and intentional failing. The investigation recorded has been carefully done, and the book contains a great deal of valuable material for the criminologist.

Das Retikulo-Endotheliale System der Schizophrenen. Von Fr. MEYER. Berlin: Karger. 1931. S. 124. Price Rm. 12.

The search for somatic changes in schizophrenia is being actively pursued, and it occurred to Dr. Meyer that in the reticulo-endothelial system lay an important, and so far neglected, field of investigation. He used the congo-red test of Adler and Reimann, and Kaufmann's method which consists in examining the cellular content of the exudate in a blister. He applied these methods also to patients with other mental disorders than schizophrenia. His conclusions were that in schizophrenia during an attack the storage function of the reticulo-endothelial system is impaired, as is also its capacity to promote resistance to irritants; disturbances in the activity of the liver cells and other metabolic disorders may be attributed to this. Somewhat similar findings were obtained in G.P.I., encephalitis lethargica and other psychoses. The work has been carefully done, but the interpretation of observations and the assumption that one is dealing with a primary rather than a derivative, unspecific phenomenon of the psychosis may be questioned.

Intelligence and Disease. By SHEPHERD DAWSON, assisted by J. C. M. CONN. London: Medical Research Council. 1931. Pp. 53. Price 1s.

The effect of illness upon the intelligence of children, as measured by the usual Binet-Simon tests, was investigated in Glasgow upon 1,000 children in hospital, healthy siblings being used as the material of comparison. Subsidiary studies on the relation of intelligence to stature were also made. The findings were that intelligence was unaffected by disease unless there were a more or less diffuse affection of the brain or of the ductless glands. It is surprising that in the work done on epileptics and encephalitics the effect of the drugs administered in these conditions does not seem to have been taken into account, particularly in regard to the results of retesting, which in the case of epilepsy are held by the author to indicate deterioration.

Baillière's Synthetic Anatomy. Part X.—The Brain. By J. E. CHEESEMAN. London: Baillière, Tindall and Cox. 1932. 12 plates. Price 3s.

These drawings resemble those already published of other parts of the body in being taken from sections in an oblique plane, the plane of one half of the brain and skull being less oblique than that of the other half. This arrangement shows more details of certain structures, but none the less adds to confusion. The more usual scheme of a series of sections in each of the three main planes is simpler and preferable. It is claimed, however, for the present sections that one obtains by one series a composite view for which at least two series in the usual planes would be necessary. It is no doubt possible to learn the gross anatomy of the brain and meninges from these drawings, and perhaps they have an additional value in that the difficulty in understanding them may serve to impress the details of the anatomy more deeply on the learner.

Histopathology of the Central Nervous System. By L. BOUMAN and S. T. BOK. Utrecht: A. Oosthoek's Publishing Co. 1932. Pp. 38, with 53 full-page plates. Price 25 florins.

In this atlas the authors have "tried to give a general survey of the histopathology of the most important diseases of the central nervous system by means of a series of micro-photographs accompanied by a short concise text." Such a method of presentation of neuropathology has definite advantages, and no less obvious defects; and within its limitations the authors have succeeded remarkably well. The photographs, which form the main part of the book, are clearly reproduced on stiff boards and should thus be of permanent value. The letterpress, although more concise than is necessary, gives clear and up-to-date descriptions of the different types of cell and their alterations in disease. The table, in which the lesions of the various inflammatory diseases of the central nervous system are contrasted, should be of special value to those with

a limited experience of these conditions. But also some amplification would have been valuable: for example, encephalitis lethargica is described as affecting chiefly the mid-brain, and little or nothing is said about the lesions which it produces in the cerebral hemispheres or the lower levels of the brain-stem.

We cannot suppress a regret that the authors did not make more generous use of their wide knowledge of neuropathology by considerable enlargement of the letterpress. Any slight increase of price which this would have entailed would certainly have been more than compensated by the increased value of the book. But as an atlas of the pathological histology of the nervous system the book is distinctly successful, and should have a definite value for those who wish to make a rapid survey of this field.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.